PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 401/02, A61K 31/415, 31/47 | A1

(11) International Publication Number: WO 99/28313

(43) International Publication Date: 10 June 1999 (10.06.99)

(21) International Application Number: PCT/US98/25352

(22) International Filing Date: 30 November 1998 (30.11.98)

(30) Priority Data:
08/985,320 4 December 1997 (04.12.97) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 08/985,320 (CON)
Filed on 4 December 1997 (04.12.97)

(71) Applicant *(for all designated States except US)*: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: CICCARONE, Terrence, M. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). HALCZENKO, Wasyl [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). HUTCHINSON, John, H. [CA/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). LUMMA, William, C., Jr. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). STOKKER, Gerald, E. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). STUMP, Craig, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). WILLIAMS, Theresa, M. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

(57) Abstract

The present invention is directed to compounds which inhibit farnesyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. The invention is further directed to chemoterapeutic compositions containing the compounds of this invention and methods for inhibiting farnesyl-protein transferase and the farnesylation of the oncogene protein Ras.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

TITLE OF THE INVENTION

INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

BACKGROUND OF THE INVENTION

The Ras protein is part of a signalling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Biological and biochemical studies of Ras action indicate that Ras functions like a G-regulatory protein. In the inactive state, Ras is bound to GDP. Upon growth factor receptor activation Ras is induced to exchange GDP for GTP and undergoes a conformational change. The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and D.M. Willumsen, *Ann. Rev. Biochem. 62*:851-891 (1993)). Mutated *ras* genes are found in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit a growth stimulatory signal.

Ras must be localized to the plasma membrane for both normal and oncogenic functions. At least 3 post-translational modifications are involved with Ras membrane localization, and all 3 modifications occur at the C-terminus of Ras. The Ras C-terminus contains a sequence motif termed a "CAAX" or "Cys-Aaa^1-Aaa^2-Xaa" box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen *et al., Nature 310*:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence for the enzymes farnesyl-protein transferase or geranylgeranyl-protein transferase, which catalyze the alkylation of the cysteine residue of the CAAX motif with a C_{15} or C_{20} isoprenoid, respectively. (S. Clarke., *Ann. Rev. Biochem. 61*:355-386 (1992); W.R. Schafer and J. Rine, *Ann. Rev. Genetics 30*:209-237 (1992)). The Ras protein is one of several proteins that are known to undergo post-translational farnesylation. Other farnesylated proteins include the Ras-

related GTP-binding proteins such as Rho, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, et al., *J. Biol. Chem. 269*, 14182 (1994) have identified a peroxisome associated protein Pxf which is also farnesylated. James, et al., have also suggested that there are farnesylated proteins of unknown structure and function in addition to those listed above.

Inhibition of farnesyl-protein transferase has been shown to block the growth of Ras-transformed cells in soft agar and to modify other aspects of their transformed phenotype. It has also been demonstrated that certain inhibitors of farnesyl-protein transferase selectively block the processing of the Ras oncoprotein intracellularly (N.E. Kohl *et al.*, *Science*, *260*:1934-1937 (1993) and G.L. James *et al.*, *Science*, *260*:1937-1942 (1993). Recently, it has been shown that an inhibitor of farnesyl-protein transferase blocks the growth of *ras*-dependent tumors in nude mice (N.E. Kohl *et al.*, *Proc. Natl. Acad. Sci U.S.A.*, *91*:9141-9145 (1994) and induces regression of mammary and salivary carcinomas in *ras* transgenic mice (N.E. Kohl *et al.*, *Nature Medicine*, 1:792-797 (1995).

Indirect inhibition of farnesyl-protein transferase *in vivo* has been demonstrated with lovastatin (Merck & Co., Rahway, NJ) and compactin (Hancock *et al.*, *ibid*; Casey *et al.*, *ibid*; Schafer *et al.*, *Science 245*:379 (1989)). These drugs inhibit HMG-CoA reductase, the rate limiting enzyme for the production of polyisoprenoids including farnesyl pyrophosphate. Farnesyl-protein transferase utilizes farnesyl pyrophosphate to covalently modify the Cys thiol group of the Ras CAAX box with a farnesyl group (Reiss *et al., Cell, 62*:81-88 (1990); Schaber *et al., J. Biol. Chem., 265*:14701-14704 (1990); Schafer *et al., Science, 249*:1133-1139 (1990); Manne *et al., Proc. Natl. Acad. Sci USA, 87*:7541-7545 (1990)). Inhibition of farnesyl pyrophosphate biosynthesis by inhibiting HMG-CoA reductase blocks Ras membrane localization in cultured cells. However, direct inhibition of farnesyl-protein transferase would be more specific and attended by fewer side effects than would occur with the required dose of a general inhibitor of isoprene biosynthesis.

Inhibitors of farnesyl-protein transferase (FPTase) have been described in two general classes. The first are analogs of farnesyl diphosphate (FPP), while the second class of inhibitors is related to the protein substrates (e.g., Ras) for the enzyme. The peptide derived inhibitors that have been described are generally cysteine containing molecules that are related to the CAAX motif that is the signal for protein prenylation. (Schaber *et al.*, *ibid*; Reiss *et. al.*, *ibid*; Reiss *et al.*, *PNAS*, *88*:732-736 (1991)). Such inhibitors may inhibit protein prenylation while serving as alternate substrates for the farnesyl-protein transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas; N.E. Kohl *et al.*, *Science*, *260*:1934-1937 (1993); Graham, et al., *J. Med. Chem.*, *37*, 725 (1994)). In general, deletion of the thiol from a CAAX derivative has been shown to dramatically reduce the inhibitory potency of the compound. However, the thiol group potentially places limitations on the therapeutic application of FPTase inhibitors with respect to pharmacokinetics, pharmacodynamics and toxicity. Therefore, a functional replacement for the thiol is desirable.

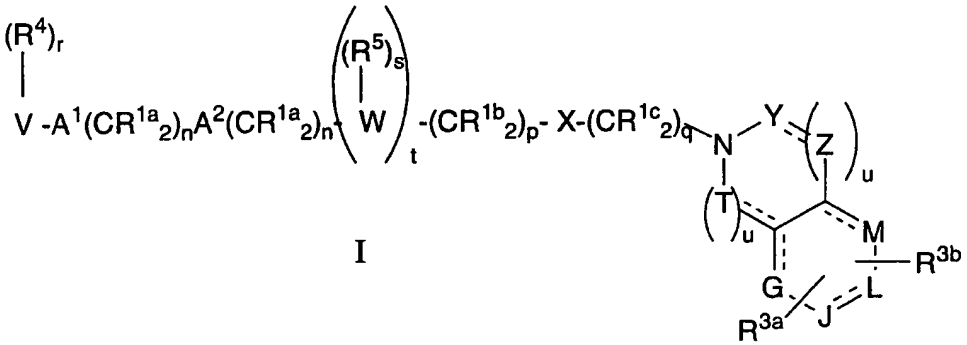
It has recently been shown that farnesyl-protein transferase inhibitors are inhibitors of proliferation of vascular smooth muscle cells and are therefore useful in the prevention and therapy of arteriosclerosis and diabetic disturbance of blood vessels (JP H7-112930). It has also recently been disclosed that certain 1,2,3,4-tetrahydroisoquinoline peptidomimetic compounds, some of which incorporate an imidazole moiety, are inhibitors of FPTase (U.S. Pat. No. 5,439,918, EP 0 618 221 A2 and EP 0 675 112 A1).

It is, therefore, an object of this invention to develop novel peptidomimetic compounds that do not have a thiol moiety, and that will inhibit farnesyl-protein transferase and thus, the post-translational farnesylation of proteins. It is a further object of this invention to develop chemotherapeutic compositions containing the compounds of this invention and methods for producing the compounds of this invention.

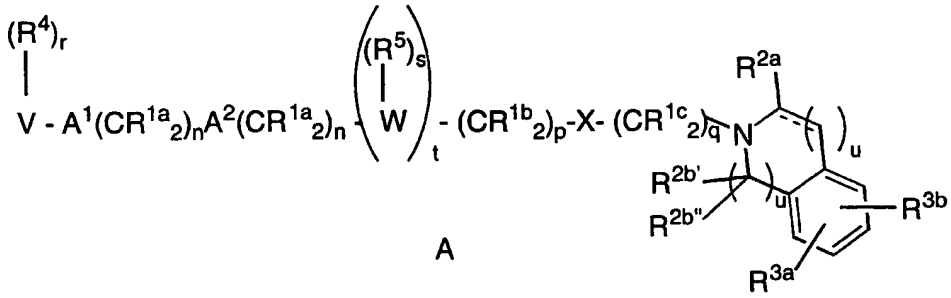
SUMMARY OF THE INVENTION

The present invention comprises peptidomimetic 1,2,3,4-tetrahydroisoquinolines and homologous compounds which inhibit farnesyl-protein transferase. Furthermore, these compounds differ from such heterocyclic compounds previously described as inhibitors of farnesyl-protein transferase with respect to the alkyl or heteroatom containing linker between the tetrahydroisoquinoline nitrogen and the imidazolyl moiety, and with respect to the lack of a thiol moiety in the instant compounds. Further contained in this invention are chemotherapeutic compositions containing these farnesyl transferase inhibitors and methods for their production.

The compounds of this invention are illustrated by the formulae I and A:



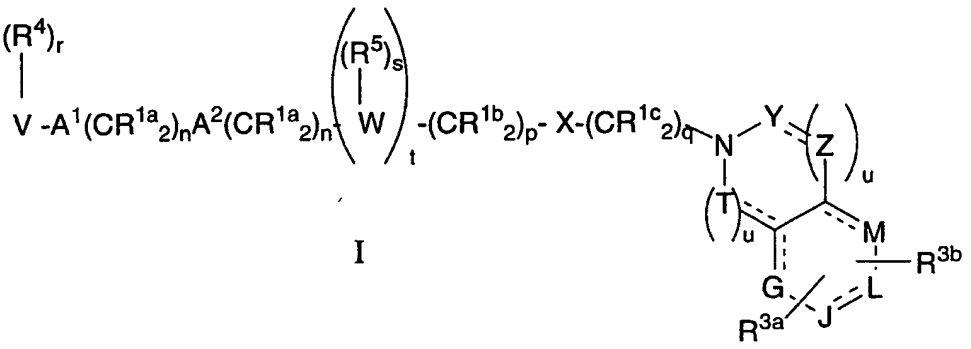
I



A

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. In a first embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula I:



I

wherein:

R^{1a}, R^{1b} and R^{1c} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) C_1-C_6 alkyl unsubstituted or substituted by unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)$-NR^8-,

provided that R^{1a} is not unsubstituted or substituted imidazolyl;

R^{2a}, $R^{2b'}$ and $R^{2b''}$ are independently hydrogen, NH_2 or $-(CR^{11}{}_2)_vA^3(CR^{12}{}_2)_wR^{13}$; or

$R^{2b'}$ and $R^{2b''}$ are combined as O;

R^{3a} and R^{3b} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-$C(NR^8)$-, CN, NO_2, $R^8C(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-$C(NR^8)$-, CN, $R^8C(O)$-, N_3, $-N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^4 is independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $R^8{}_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NH$-, CN, H_2N-$C(NH)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^8OC(O)NH$-,

provided that R^4 is not unsubstituted or substituted imidazolyl;

R^5 is independently selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-C-(NR^8)-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl, unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

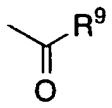
R^{10} is selected from: H; $R^8C(O)$-; $R^9S(O)_m$-; unsubstituted or substituted C_1-$_4$ alkyl, unsubstituted or substituted C_3-$_6$ cycloalkyl, unsubstituted or substituted heterocycle, unsubstituted or substituted aryl, substituted aroyl, unsubstituted or substituted heteroaroyl, substituted arylsulfonyl, unsubstituted or substituted heteroarylsulfonyl, wherein the substituted group is substituted with one or two substituents selected from:

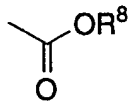
a) C_1-$_4$ alkoxy,

b) aryl or heterocycle,

c) halogen,

d) HO,

e)  ,

f)  ,

g) $-S(O)_mR^9$,

h) $N(R^8)_2$, or
i) C_{3-6} cycloalkyl;

R^{11} and R^{12} are independently selected from:

a) hydrogen,
b) C_1-C_6 alkyl unsubstituted or substituted by C_2-C_{20} alkenyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, N_3, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-,
c) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_{20} alkenyl, halogen, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and
d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C_3-C_{10} cycloalkyl;

R^{13} is selected from:

a) hydrogen,
b) substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_{20} alkenyl, C_2-C_{20} alkynyl, C_1-C_{20} perfluoroalkyl, allyloxy, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $R^8{}_2N$-$C(NR^8)$-, $R^8C(O)$-, N_3, $-N(R^8)_2$, $(R^9)_2NC(O)$- or $R^9OC(O)NR^8$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_{20} alkenyl, C_2-C_{20} alkynyl, C_2-C_{20} perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NH$-, CN, H_2N-$C(NH)$-, $R^8C(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NH$-;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^8-, -NR^8C(O)-, O, -N(R^8)-, -S(O)$_2$N(R^8)-, -N(R^8)S(O)$_2$-, or -S(O)$_m$;

A^3 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, -S(O)$_2$N(R^{10})-, -N(R^{10})S(O)$_2$-, or S(O)$_m$;

G, J, L and M are independently selected from: CH_y or N;

T is selected from: N, $CR^{2b'}$ or $CR^{2b'}R^{2b''}$;

V is selected from:

a) hydrogen,
b) heterocycle,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is S(O)$_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is S(O)$_m$;
and provided that V is not imidazolyl;

W is a heterocycle;

X is a bond, -S(O)$_m$-, O or -C(=O)-;

Y is selected from: CR^{2a}, C=O, C=NH or N;

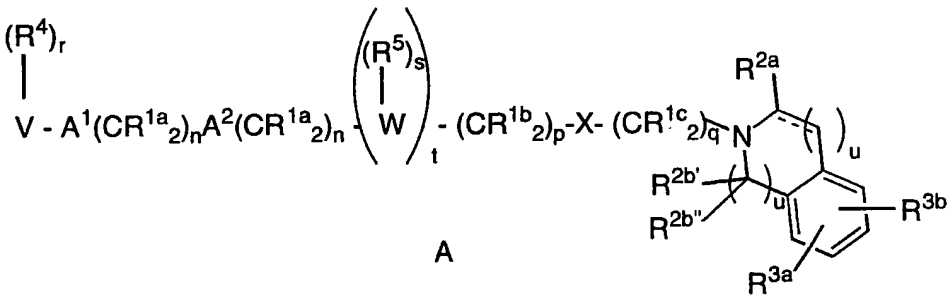
Z is selected from: CR^{2a}, C=O or N;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4;
q is 0, 1, 2, 3 or 4, provided that q is not 0 or 1 if X is O;
r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 1 or 2;
t is independently 0 or 1;
u is independently 0,1 or 2;
v is 0, 1, 2, 3 or 4, provided that v is not 0 when A^3 is $-NR^{10}C(O)-$, O, $-N(R^{10})-$, $-S(O)_2N(R^{10})-$, $-N(R^{10})S(O)_2-$, or $S(O)_m$;
w is 0, 1, 2, 3 or 4; and
y is 1 or 2;
the dashed lines represent optional double bonds;

or an optical isomer or a pharmaceutically acceptable salt thereof.

In another embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula A:



A

wherein:
R^{1a}, R^{1b} and R^{1c} are independently selected from:

a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_m-$, $R^8C(O)NR^8-$, CN, NO_2,

$(R^8)_2N$-C(=NR^8)-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) C_1-C_6 alkyl unsubstituted or substituted by unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, $(R^8)_2N$-C(=NR^8)-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)$-NR^8-,

provided that R^{1a} is not unsubstituted or substituted imidazolyl;

R^{2a}, $R^{2b'}$ and $R^{2b''}$ are independently hydrogen or -$(CR^{11}_2)_vA^3(CR^{12}_2)_wR^{13}$; or
$R^{2b'}$ and $R^{2b''}$ are combined as O;

R^{3a} and R^{3b} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, R^8_2N-C(=NR^8)-, CN, NO_2, $R^8C(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, R^8_2N-C(=NR^8)-, CN, $R^8C(O)$-, N_3, -$N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^4 is independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $R^8{}_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NH$-, CN, H_2N-$C(NH)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^8OC(O)NH$-,

provided that R^4 is not unsubstituted or substituted imidazolyl;

R^5 is independently selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-C-(NR^8)-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl, unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

R^{10} is selected from: H; $R^8C(O)$-; $R^9S(O)_m$-; unsubstituted or substituted C_{1-4} alkyl, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted heterocycle, unsubstituted or substituted aryl, substituted aroyl, unsubstituted or substituted heteroaroyl, substituted arylsulfonyl, unsubstituted or substituted heteroarylsulfonyl,

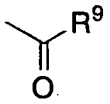
wherein the substituted group is substituted with one or two substituents selected from:

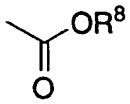
a) C_{1-4} alkoxy,

b) aryl or heterocycle,

c) halogen,

d) HO,

e)  ,

f)  ,

g) $-S(O)_mR^9$,

h) $N(R^8)_2$, or

i) C_{3-6} cycloalkyl;

R^{11} and R^{12} are independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl unsubstituted or substituted by C_2-C_{20} alkenyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, N_3, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_{20} alkenyl, halogen, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C_3-C_{10} cycloalkyl;

R^{13} is selected from:

a) hydrogen,

b) substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_{20} alkenyl, C_2-C_{20} alkynyl, C_1-C_{20} perfluoroalkyl, allyloxy, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $R^8{}_2N$-$C(NR^8)$-, $R^8C(O)$-, N_3, -$N(R^8)_2$, $(R^9)_2NC(O)$- or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_{20} alkenyl, C_2-C_{20} alkynyl, C_2-C_{20} perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NH$-, CN, H_2N-$C(NH)$-, $R^8C(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NH$-;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^8$-, -$NR^8C(O)$-, O, -$N(R^8)$-, -$S(O)_2N(R^8)$-, -$N(R^8)S(O)_2$-, or -$S(O)_m$;

A^3 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

V is selected from:

a) hydrogen,

b) heterocycle,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

and provided that V is not imidazolyl;

W is a heterocycle;

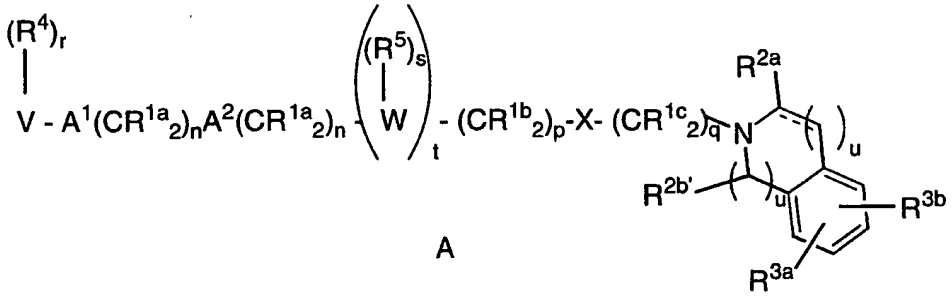
X is a bond, -S(O)m-, O or -C(=O)-;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
q is 0, 1, 2, 3 or 4, provided that q is not 0 or 1 if X is O;
r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 1 or 2;
t is 0 or 1;
u is independently 0,1 or 2;
v is 0, 1, 2, 3 or 4, provided that v is not 0 when A^3 is $-NR^{10}C(O)-$, O, $-N(R^{10})-$, $-S(O)_2N(R^{10})-$, $-N(R^{10})S(O)_2-$, or $S(O)_m$;
w is 0, 1, 2, 3 or 4; and

the dashed lines represent optional double bonds;

or an optical isomer or a pharmaceutically acceptable salt thereof.

A preferred embodiment of the compounds of this invention is illustrated by the following formula:



A

wherein:

R^{1a} and R^{1c} are independently selected from: hydrogen, C_3-C_{10} cycloalkyl, R^8O-, -$N(R^8)_2$, F or C_1-C_6 alkyl;

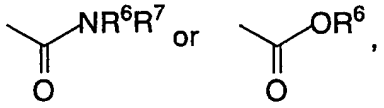
R^{1b} is independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_6 cycloalkyl, R^8O-, -$N(R^8)_2$ or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by unsubstituted or substituted aryl, heterocycle, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, R^8O-, or -$N(R^8)_2$;

R^{2a} and $R^{2b'}$ are independently selected from: H; C_1-C_6 alkyl,



R^{3a} and R^{3b} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-$C(NR^8)$-, CN, NO_2, $R^8C(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-$C(NR^8)$-, CN, $R^8C(O)$-, N_3, -$N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^4 is independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^5 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^6 and R^7 are independently selected from:

H; C_1-$_4$ alkyl, C_3-$_6$ cycloalkyl, aryl, heterocycle, unsubstituted or substituted with one or two:

a) C_1-$_4$ alkoxy,

b) halogen, or

c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle,

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^8-, O, -$N(R^8)$-, or -$S(O)_m$;

V is selected from:

a) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, indolyl, quinolinyl, isoquinolinyl, and thienyl, and

b) aryl;

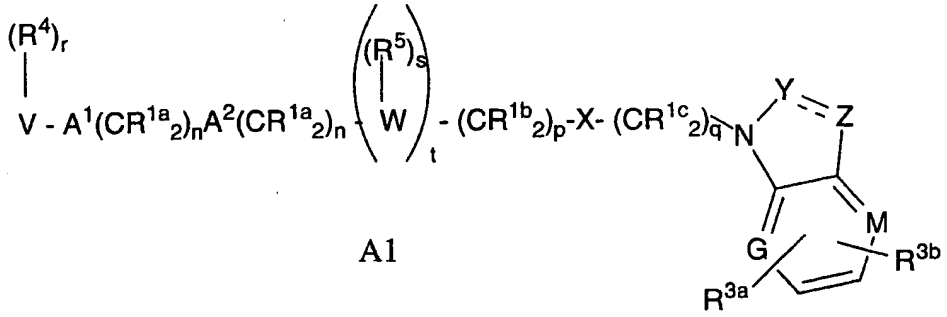
W is a heterocycle selected from pyrrolidinyl, triazolyl, imidazolyl, pyridinyl, thiazolyl, indolyl, quinolinyl, or isoquinolinyl;

X is a bond, -$S(O)_m$-, O or -C(=O)-;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 1, 2 or 3;
q is 0, 1 or 2, provided that q is not 0 or 1 if X is O;
r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 1 or 2;
t is 1; and
u is independently 0 or 1;

or an optical isomer or a pharmaceutically acceptable salt thereof.

In another more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula A1:



A1

wherein

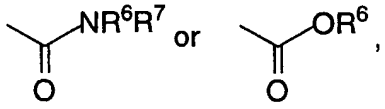
R^{1a} and R^{1c} are independently selected from: hydrogen, C_3-C_{10} cycloalkyl, R^8O-, -$N(R^8)_2$, F or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_6 cycloalkyl, R^8O-, -$N(R^8)_2$ or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by unsubstituted or substituted aryl, heterocycle, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, R^8O-, or -$N(R^8)_2$;

R^{2a} is selected from: H; C_1-C_6 alkyl, NH_2  ,

R^{3a} and R^{3b} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-$C(NR^8)$-, CN, NO_2, $R^8C(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-$C(NR^8)$-, CN, $R^8C(O)$-, N_3, -$N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^4 is independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^5 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^6 and R^7 are independently selected from:
H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with one or two:

a) C_{1-4} alkoxy,

b) halogen, or
c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle,

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^8-, -NR^8C(O)-, O, -N(R^8)-, -S(O)$_2$N(R^8)-, -N(R^8)S(O)$_2$-, or -S(O)$_m$;

G and M are independently selected from: CH_y or N;

V is selected from:

a) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, indolyl, quinolinyl, isoquinolinyl, and thienyl, and
b) aryl;

W is a heterocycle selected from pyrrolidinyl, triazolyl, imidazolyl, pyridinyl, thiazolyl, indolyl, quinolinyl, or isoquinolinyl;

X is a bond, -S(O)$_m$-, O or -C(=O)-;

Y is selected from: CR^{2a}, C=O, C=NH or N;

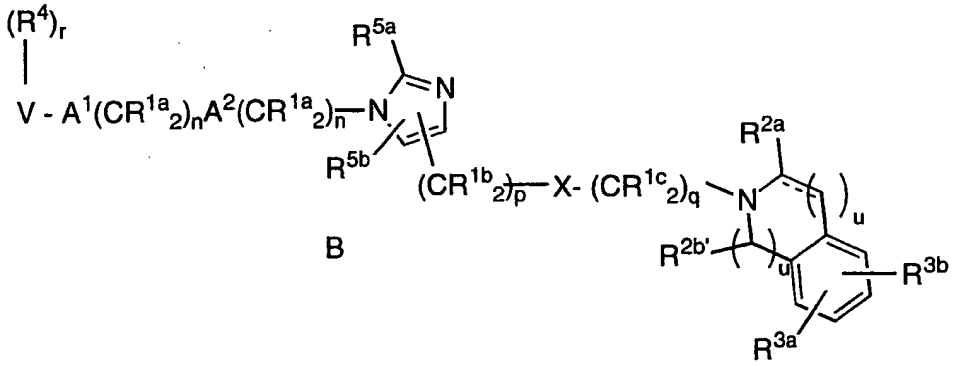
Z is selected from: CR^{2a}, C=O or N;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 1, 2 or 3;
q is 0, 1 or 2, provided that q is not 0 or 1 if X is O;

r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 1 or 2;
t is 1; and
y is 1 or 2;

or an optical isomer or a pharmaceutically acceptable salt thereof.

Another preferred embodiment of the compounds of this invention are illustrated by the formula B:



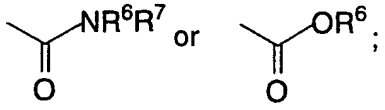
B

wherein:

R^{1a} and R^{1c} are independently selected from: hydrogen, C_3-C_{10} cycloalkyl, R^8O-, -$N(R^8)_2$, F or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, R^8O-, -$N(R^8)_2$, F or C_2-C_6 alkenyl,
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, R^8O- and -$N(R^8)_2$;

R^{2a} and $R^{2b'}$ are independently selected from selected from: H; C_1-C_6 alkyl,  ;

R^{3a} and R^{3b} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-$C(NR^8)$-, CN, NO_2, $R^8C(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-$C(NR^8)$-, CN, $R^8C(O)$-, N_3, -$N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^4 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^{5a} and R^{5b} are independently hydrogen, C_1-C_6 alkyl, cyclopropyl, trifluoromethyl and halogen;

R^6 and R^7 are independently selected from:
H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with one or two:
a) C_{1-4} alkoxy,
b) halogen, or
c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^8-, O, -$N(R^8)$-, or -$S(O)_m$;

V is selected from:
a) hydrogen,
b) heterocycle selected from pyrrolidinyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl, and

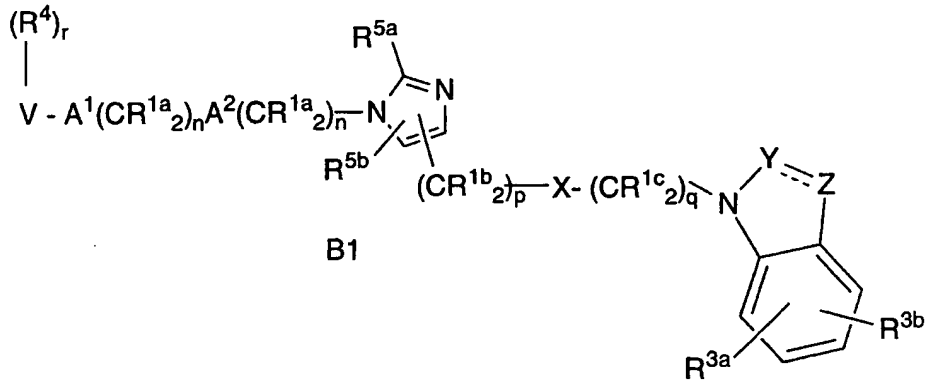
provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

X is a bond, -$S(O)_m$-, O or -C(=O)-;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
q is 0, 1 or 2, provided that q is not 0 or 1 if X is O;
r is 0 to 5, provided that r is 0 when V is hydrogen; and
u is independently 0 or 1;

or an optical isomer or pharmaceutically acceptable salt thereof.

In another more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula B1:



B1

wherein

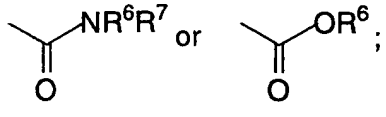
R^{1a} and R^{1c} are independently selected from: hydrogen, C_3-C_{10} cycloalkyl, R^8O-, -$N(R^8)_2$, F or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, R^8O-, -$N(R^8)_2$, F or C_2-C_6 alkenyl,
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from

unsubstituted or substituted aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, R^8O- and -$N(R^8)_2$;

R^{2a} is selected from selected from: H; C_1-C_6 alkyl,



NH_2,

R^{3a} and R^{3b} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-$C(NR^8)$-, CN, NO_2, $R^8C(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-$C(NR^8)$-, CN, $R^8C(O)$-, N_3, -$N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^4 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^{5a} and R^{5b} are independently hydrogen, C_1-C_6 alkyl, cyclopropyl, trifluoromethyl and halogen;

R^6 and R^7 are independently selected from:
H; C_1-$_4$ alkyl, C_3-$_6$ cycloalkyl, aryl, heterocycle, unsubstituted or substituted with one or two:
a) C_1-$_4$ alkoxy,
b) halogen, or
c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^8$-, O, -$N(R^8)$-, or -$S(O)_m$;

V is selected from:
a) hydrogen,
b) heterocycle selected from pyrrolidinyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen

if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

X is a bond, $-S(O)_m-$, O or -C(=O)-;

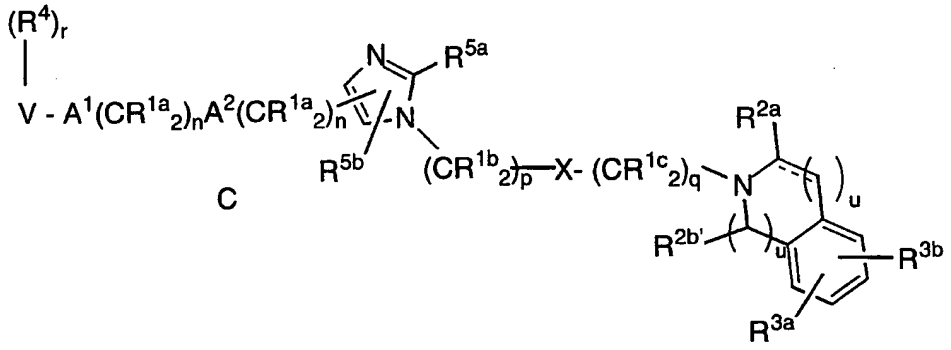
Y is selected from: CR^{2a}, C=O, C=NH or N;

Z is selected from: CR^{2a}, C=O or N;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 1, 2 or 3;
q is 0, 1 or 2, provided that q is not 0 or 1 if X is O;
r is 0 to 5, provided that r is 0 when V is hydrogen; and
y is 1 or 2;

or an optical isomer or pharmaceutically acceptable salt thereof.

Another preferred embodiment of the compounds of this invention are illustrated by the formula C:



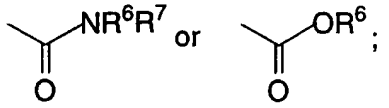
C

wherein:

R^{1a} and R^{1c} are independently selected from: hydrogen, C_3-C_{10} cycloalkyl, R^8O-, $-N(R^8)_2$, F or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, R^8O-, -$N(R^8)_2$, F or C_2-C_6 alkenyl,
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, R^8O- and -$N(R^8)_2$;

R^{2a} and $R^{2b'}$ are independently selected from selected from: H; C_1-C_6 alkyl,  ;

R^{3a} and R^{3b} are independently selected from:
a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-$C(NR^8)$-, CN, NO_2, $R^8C(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-,
c) unsubstituted C_1-C_6 alkyl,
d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-$C(NR^8)$-, CN, $R^8C(O)$-, N_3, -$N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^4 is independently selected from:
a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^{5a} and R^{5b} are independently hydrogen, C_1-C_6 alkyl, cyclopropyl, trifluoromethyl and halogen;

R^6 and R^7 are independently selected from:
H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with one or two:
a) C_{1-4} alkoxy,
b) halogen, or
c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, $-C(O)NR^8$-, O, -$N(R^8)$-, or -$S(O)_m$;

V is selected from:
a) hydrogen,
b) heterocycle selected from pyrrolidinyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,
c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl, and

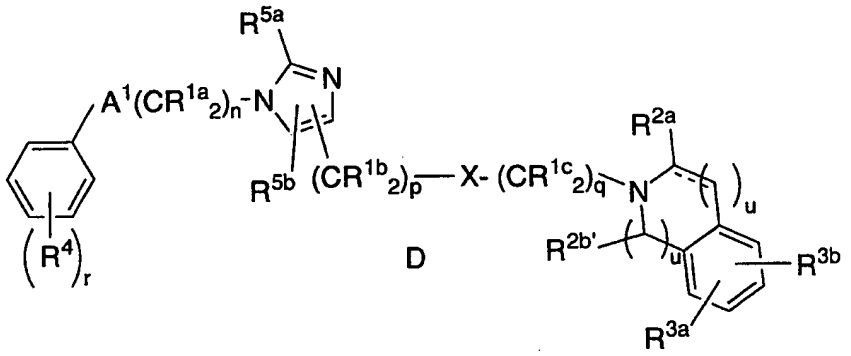
provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

X is a bond, $-S(O)_m-$, O or $-C(=O)-$;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond or O;
q is 0, 1 or 2, provided that q is not 0 or 1 if X is O;
r is 0 to 5, provided that r is 0 when V is hydrogen; and
u is independently 0 or 1;

or an optical isomer or pharmaceutically acceptable salt thereof.

In a more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula D:



D

wherein:

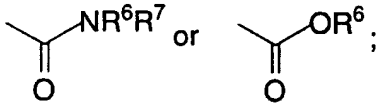
R^{1a} and R^{1c} are independently selected from: hydrogen, C_3-C_{10} cycloalkyl or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, R^8O-, -$N(R^8)_2$, F or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, R^8O-, or -$N(R^8)_2$;

R^{2a} and $R^{2b'}$ are independently selected from selected from: H; C_1-C_6 alkyl,  ;

R^{3a} and R^{3b} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-$C(NR^8)$-, CN, NO_2, $R^8C(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-$C(NR^8)$-, CN, $R^8C(O)$-, N_3, -$N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^4 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^{5a} and R^{5b} are independently hydrogen, ethyl, cyclopropyl or methyl;

R^6 and R^7 are independently selected from:
H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with one or two:
a) C_{1-4} alkoxy,
b) halogen, or
c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

A^1 is selected from: a bond, -C(O)-, O, $-N(R^8)$-, or $-S(O)_m$;

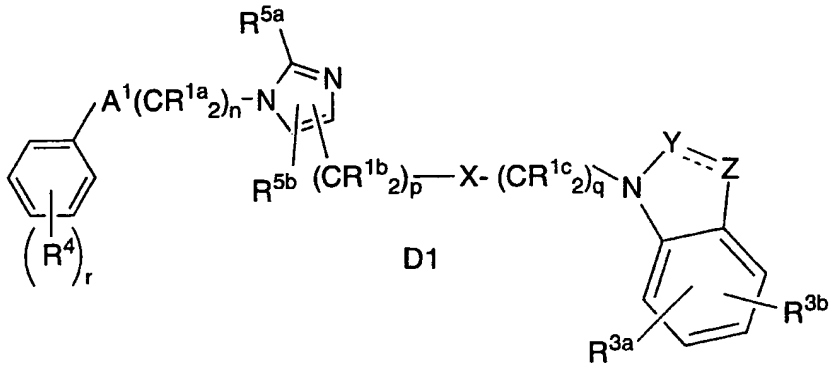
X is a bond, $-S(O)_m$-, O or -C(=O)-;

n is 0, 1 or 2; provided that n is not 0 or 1 if A^1 is a bond, O, $-N(R^8)$-, or $S(O)_m$;
m is 0, 1 or 2;
p is 0, 1, 2, 3 or 4;
q is 0, 1 or 2, provided that q is not 0 or 1 if X is O;
r is 1 or 2; and

u is independently 0 or 1;

or an optical isomer or pharmaceutically acceptable salt thereof.

In another more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula D1:



D1

wherein

R^{1a} and R^{1c} are independently selected from: hydrogen, C_3-C_{10} cycloalkyl or C_1-C_6 alkyl;

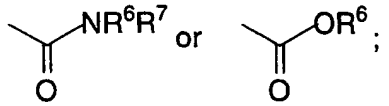
R^{1b} is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, R^8O-, -$N(R^8)_2$, F or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, R^8O-, or -$N(R^8)_2$;

R^{2a} is selected from selected from: H; C_1-C_6 alkyl, NH_2,



R^{3a} and R^{3b} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-$C(NR^8)$-, CN, NO_2, $R^8C(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-$C(NR^8)$-, CN, $R^8C(O)$-, N_3, $-N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^4 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^{5a} and R^{5b} are independently hydrogen, ethyl, cyclopropyl or methyl;

R^6 and R^7 are independently selected from:

H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle,

unsubstituted or substituted with one or two:
a) C_{1-4} alkoxy,
b) halogen, or
c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

A^1 is selected from: a bond, -C(O)-, O, -N(R^8)-, or -S(O)$_m$;

X is a bond, -S(O)$_m$-, O or -C(=O)-;

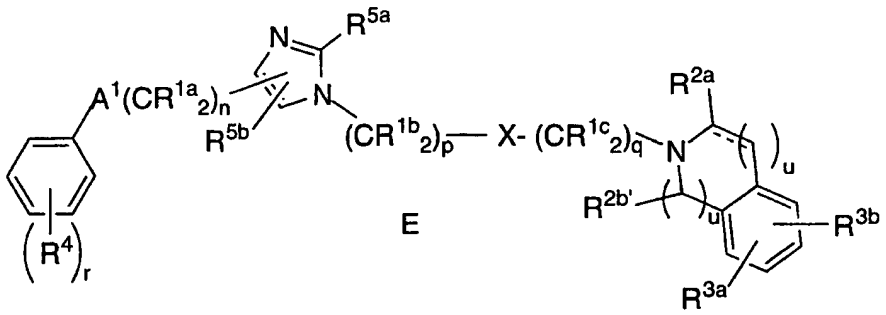
Y is selected from: CR^{2a}, C=NH or N;

Z is selected from: CR^{2a}, or N; provided that at least Y or Z is N;

n is 0, 1 or 2; provided that n is not 0 or 1 if A^1 is a bond, O, -N(R^8)-, or S(O)$_m$;
m is 0, 1 or 2;
p is 0, 1, 2, 3 or 4;
q is 0, 1 or 2, provided that q is not 0 or 1 if X is O;
r is 1 or 2; and
y is 1 or 2;

or an optical isomer or pharmaceutically acceptable salt thereof.

In another more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula E:



E

wherein:

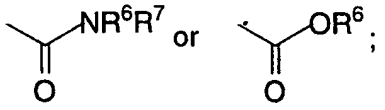
R^{1a} and R^{1c} are independently selected from: hydrogen, R^8O-, $-N(R^8)_2$, F, C_3-C_{10} cycloalkyl or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, R^8O-, $-N(R^8)_2$, F or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, R^8O-, or $-N(R^8)_2$;

R^{2a} and $R^{2b'}$ are independently selected from selected from: H; C_1-C_6 alkyl,  ;

R^{3a} and R^{3b} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-

$C(NR^8)$-, CN, NO_2, $R^8C(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-$C(NR^8)$-, CN, $R^8C(O)$-, N_3, $-N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^4 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^{5a} and R^{5b} are independently hydrogen, ethyl, cyclopropyl or methyl;

R^6 and R^7 are independently selected from:

H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with one or two:

a) C_{1-4} alkoxy,

b) halogen, or

c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

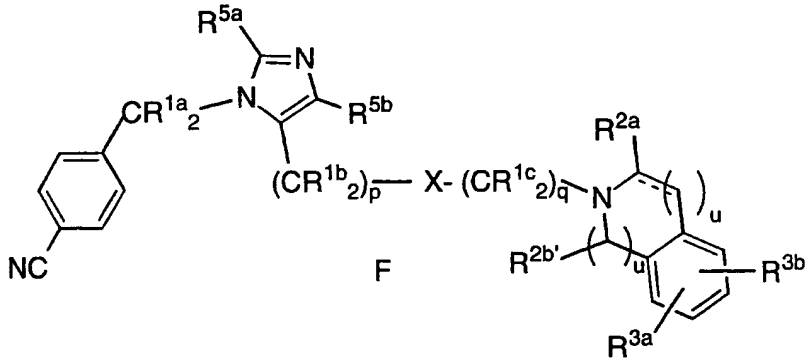
R^9 is independently selected from C_1-C_6 alkyl and aryl;

X is a bond, -S(O)$_m$-, O or -C(=O)-;

n is 0 or 1;
m is 0, 1 or 2;
p is 0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond or O;
q is 0, 1 or 2, provided that q is not 0 or 1 if X is O;
r is 1 or 2; and
u is independently 0 or 1;

or an optical isomer or pharmaceutically acceptable salt thereof.

In a further embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula F:



F

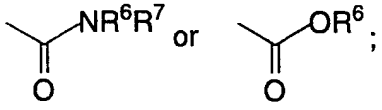
wherein:

R^{1a} and R^{1c} are independently selected from: hydrogen, C_3-C_{10} cycloalkyl or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, R^8O-, -$N(R^8)_2$ or F,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, R^8O-, or -$N(R^8)_2$;

R^{2a} and $R^{2b'}$ are independently selected from selected from: H; C_1-C_6 alkyl,  ;

R^{3a} and R^{3b} are independently selected from:
a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-$C(NR^8)$-, CN, NO_2, $R^8C(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-,
c) unsubstituted C_1-C_6 alkyl,
d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-$C(NR^8)$-, CN, $R^8C(O)$-, N_3, -$N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^{5a} and R^{5b} are independently hydrogen, ethyl, cyclopropyl or methyl;

R^6 and R^7 are independently selected from:
H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with one or two:
a) C_{1-4} alkoxy,
b) halogen, or

c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

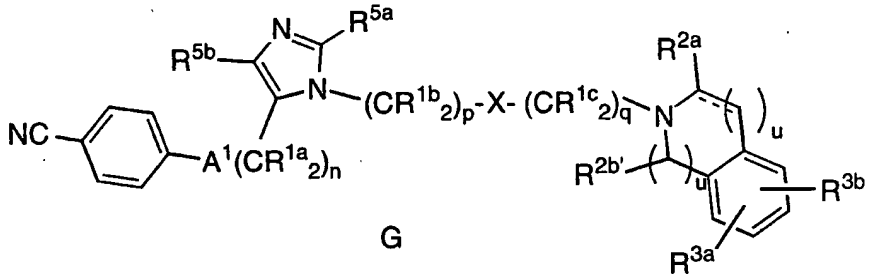
R^9 is independently selected from C_1-C_6 alkyl and aryl;

X is a bond, -S(O)m-, O or -C(=O)-;

m is 0, 1 or 2;
p is 0, 1, 2, 3 or 4;
q is 0, 1 or 2, provided that q is not 0 or 1 if X is O; and
u is independently 0 or 1;

or an optical isomer or pharmaceutically acceptable salt thereof.

In a further embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula G:



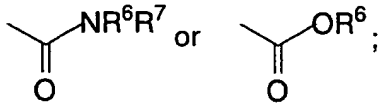
G

wherein:

R^{1a} and R^{1c} are independently selected from: hydrogen, R^8O-, -$N(R^8)_2$, F, C_3-C_{10} cycloalkyl or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle or C_3-C_{10} cycloalkyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, R^8O-, or $-N(R^8)_2$;

R^{2a} and $R^{2b'}$ are independently selected from selected from: H; C_1-C_6 alkyl,  or ;

R^{3a} and R^{3b} are independently selected from:
a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-$C(NR^8)$-, CN, NO_2, $R^8C(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-,
c) unsubstituted C_1-C_6 alkyl,
d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-$C(NR^8)$-, CN, $R^8C(O)$-, N_3, $-N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^{5a} and R^{5b} are independently hydrogen, ethyl, cyclopropyl or methyl;

R^6 and R^7 are independently selected from:
H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with one or two:
a) C_{1-4} alkoxy,

b) halogen, or
c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

A^1 is selected from: a bond, -C(O)-, O, -N(R^8)-, or -S(O)$_m$;

X is a bond, -S(O)$_m$-, O or -C(=O)-;

m is 0, 1 or 2;
n is 0, 1 or 2; provided that n is not 0 if A^1 is a bond, O, -N(R^8)-, or S(O)$_m$;
p is 1, 2 or 3;
q is 0, 1 or 2, provided that q is not 0 or 1 if X is O; and
u is independently 0 or 1;

or an optical isomer or pharmaceutically acceptable salt thereof.

The preferred compounds of this invention are as follows:

7-Bromo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

2-(1-(4-Cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

5,7-Dichloro-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

3(S)-Carboethoxy-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

3(R)-Carboethoxy-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

7-Nitro-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

7-Amino-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline tris

7-Acetamido-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

7-Iodo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

5-Bromo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

5-(2,4-Dichlorophenyl)-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

5-(4-Cyanobenzyl) -2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

5-(2-(3-Tolyl)vinyl)-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

5-(2-(3-Tolyl)ethyl)-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

7-Phenyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

7-(2-Tolyl)-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

N-(2,3-Dimethylphenyl)-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxamide

N-(3-Chlorobenzyl) 2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxamide

N-(3-Chlorobenzyl),N-methyl 2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxamide

N-(2,3-Dimethylphenyl)-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline-3(R)-carboxamide

3(S)-Carboethoxy-7-phenyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

3(S)-Carboxylic acid-7-phenyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

N-(3-chlorobenzyl) 7-phenyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline-3(s)-carboxamide

3(S)-Hydroxymethyl-7-phenyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

1(R,S)-n-Butyl-7-bromo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

1-(1-(4-Cyanobenzyl)-5-imidazolylmethyl)indole

5-Bromo-1-(1-(4-cyanobenzyl)-5-imidazolylmethyl)indole

4-Bromo-1-(1-(4-cyanobenzyl)-5-imidazolylmethyl)indole

4-Phenyl-1-(1-(4-cyanobenzyl)-5-imidazolylmethyl)indole

4-(2-Methylphenyl)-1-(1-(4-cyanobenzyl)-5-imidazolylmethyl)indole

6-Bromo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-3,4-dihydro-1(1H)-isoquinolinone

6-Bromo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

7-Bromo-2-(1-(4-cyanobenzyl)-5-imidazolylacetyl)-1,2,3,4-tetrahydroisoquinoline

5-Chloro-2-carboethoxy-1-(1-(4-cyanobenzyl)-5-imidazolylmethyl)indole

1-(4-cyanobenzyl)-5-(1-indolinylmethyl)imidazole
1-(4-cyanobenzyl)-5-(1-indazolylmethyl)imidazole

1-(4-cyanobenzyl)-5-(1-tetrahydroquinolinylmethyl)imidazole

5-(1-benzotriazolylmethyl)-1-(4-cyanobenzyl)imidazole

5-(1-benzoimidazolylmethyl)-1-(4-cyanobenzyl)imidazole

5-[1-(7-azaindolyl)methyl]-1-(4-cyanobenzyl)imidazole
5-[1-(4-azabenzimidazolyl)methyl]-1-(4-cyanobenzyl)imidazole

1-(4-cyanobenzyl)-5-(2-tetrahydroisoquinolinylmethyl)imidazole

5-(2-benzotriazolylmethyl)-1-(4-cyanobenzyl)imidazole

1-(4-cyanobenzyl)-5-(1-isatinylmethyl)imidazole

5-[1-(5-azabenzimidazolyl)methyl]-1-(4-cyanobenzyl)imidazole

5-[3-(5-azabenzimidazolyl)methyl]-1-(4-cyanobenzyl)imidazole

4-{5-[4-(3-Bromophenyl)-4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridin-1-ylmethyl]imidazol-1-ylmethyl}benzonitrile

6,7-Dimethoxy-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)1,2,3,4-tetrahydroisoquinoline

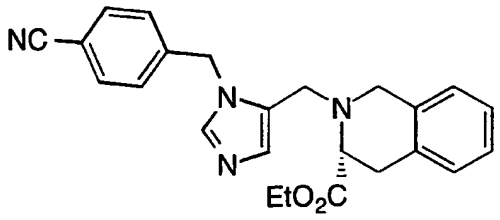
1(R,S)-(2-Phenethyl)-6-methoxy-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline
1-(4-Cyanobenzyl)-5-(2-amino-1 -benzimidazolylmethyl)imidazole

1-(4'-cyanobenzyl)-5-(2-amino-1-(3-benzyl-2-imino-1-benzimidazolylmethyl)imidazole

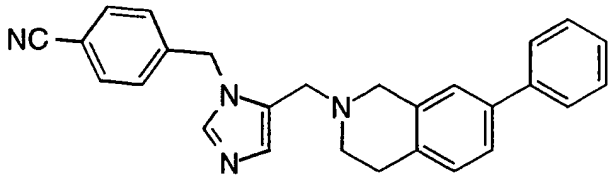
or an optical isomer or a pharmaceutically acceptable salt thereof.

Specific examples of the compounds of the invention are:

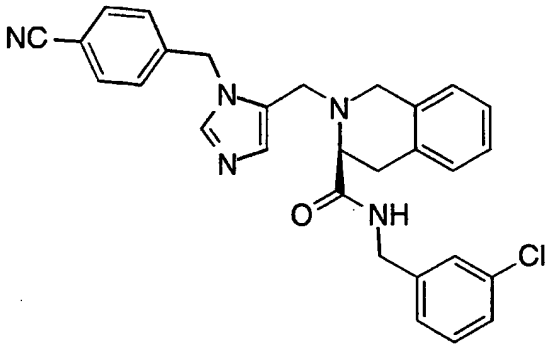
3(R)-Carboethoxy-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline



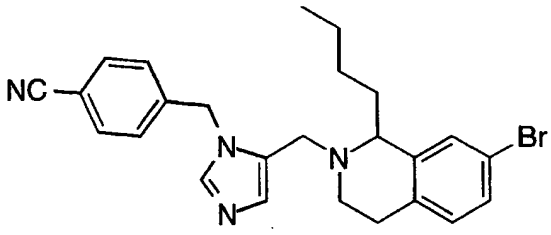
7-Phenyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline



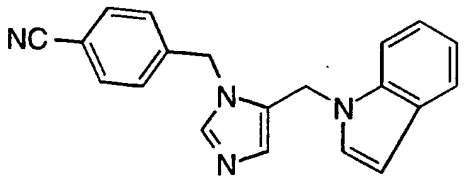
N-(3-Chlorobenzyl) 2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxamide



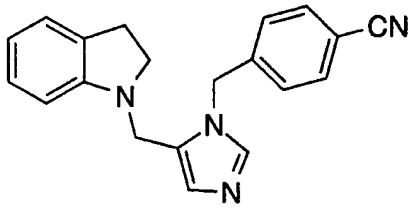
1(R,S)-n-Butyl-7-bromo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline



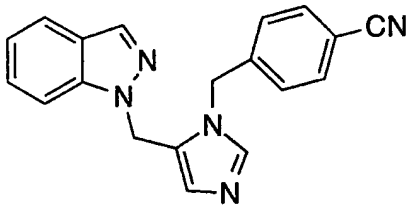
1-(1-(4-Cyanobenzyl)-5-imidazolylmethyl)indole



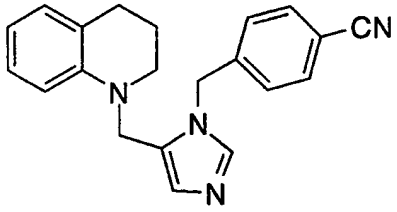
1-(4-cyanobenzyl)-5-(1-indolinylmethyl)imidazole



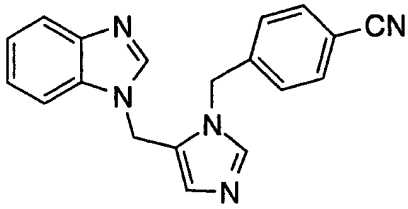
1-(4-cyanobenzyl)-5-(1-indazolylmethyl)imidazole



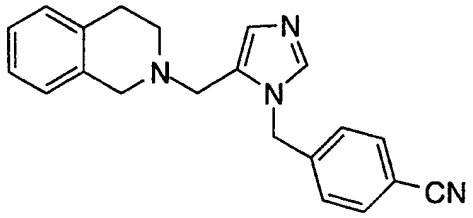
1-(4-cyanobenzyl)-5-(1-tetrahydroquinolinylmethyl)imidazole



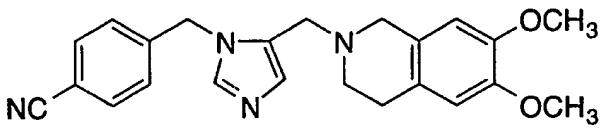
5-(1-benzoimidazolylmethyl)-1-(4-cyanobenzyl)imidazole



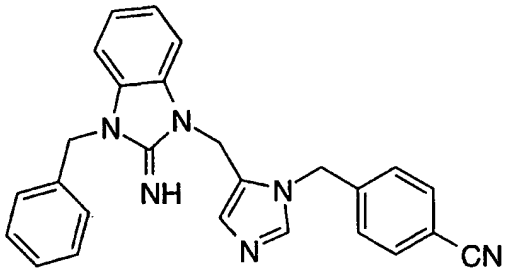
1-(4-cyanobenzyl)-5-(2-tetrahydroisoquinolinylmethyl)imidazole



6,7-Dimethoxy-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)1,2,3,4-tetrahydroisoquinoline



1-(4-Cyanobenzyl)-5-(2-amino-1-(3-benzyl-2-imino-1-benzimidazolylmethyl)imidazole



or an optical isomer or a pharmaceutically acceptable salt thereof.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. When any variable (e.g. aryl, heterocycle, R^{1a}, R^4 etc.) occurs more than one time in any constituent, its definition on each occurence is independent at every

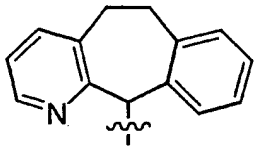
other occurence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Halogen" or "halo" as used herein means fluoro, chloro, bromo and iodo.

As used herein, "aryl" is intended to mean any stable monocyclic, bicyclic or tricyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of monocyclic and bicyclic aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl. Examples of tricyclic aryl elements include 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl (which is also known as dibenzylsuberyl), 9-fluorenyl and 9,10-dihydroanthracen-9-yl. Preferably, "aryl" is a monocyclic or bicyclic carbon ring.

The term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring or stable 13- to 15-membered tricyclic heterocyclic ring, which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of monocyclic and bicyclic heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl,

isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, 2-oxopyrrolidinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, and thienyl. Examples of tricyclic heterocyclic elements include, but are not limited to, 6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, 9,10-dihydro-4H-3-thia-benzo[f]azulen-4-yl and 9-xanthenyl. The 6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine moiety has the following structure:



Preferably, "heterocyclic" is a monocyclic or bicyclic moiety.

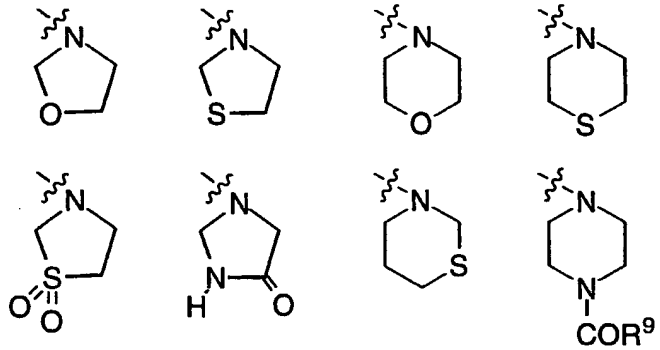
As used herein, "heteroaryl" is intended to mean any stable monocyclic, bicyclic or tricyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic and wherein from one to four carbon atoms are replaced by heteroatoms selected from the group consisting of N, O, and S. Examples of monocyclic and bicyclic heteroaryl elements include, but are not limited to, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiazolyl, thienofuryl, thienothienyl, and thienyl. Examples of tricyclic heteroaryl elements include, but are not limited to, 6,11-dihydro-5H-

benzo[5,6]cyclohepta[1,2-b]pyridine. Preferably, "heteroaryl" is a monocyclic or bicyclic moiety.

As used herein, the terms "substituted aryl", "substituted heterocycle" and "substituted cycloalkyl" are intended to include the cyclic group containing from 1 to 3 substitutents in addition to the point of attachment to the rest of the compound. Such substitutents are preferably selected from the group which includes but is not limited to F, Cl, Br, CF_3, NH_2, $N(C_1\text{-}C_6$ alkyl$)_2$, NO_2, CN, (C_1-C_6 alkyl)O-, -OH, (C_1-C_6 alkyl)S(O)$_m$-, (C_1-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, (C_1-C_6 alkyl)C(O)-, (C_1-C_6 alkyl)OC(O)-, N_3,(C_1-C_6 alkyl)OC(O)NH- and C_1-C_{20} alkyl.

When R^6 and R^7 or R^7 and R^{7a} are combined to form a ring, cyclic amine moieties are formed. Examples of such cyclic moieties include, but are not limited to:

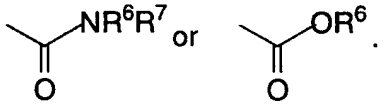
In addition, such cyclic moieties may optionally include another heteroatom(s). Examples of such heteroatom-containing cyclic amine moieties include, but are not limited to:



Lines drawn into the ring systems from substituents (such as from R^2, R^3, R^4 etc.) indicate that the indicated bond may be attached to any of the substitutable ring carbon or nitrogen atoms.

Preferably, R^{1a} and R^{1b} are independently selected from:
hydrogen, $-N(R^8)_2$, $R^8C(O)NR^8-$ or C_1-C_6 alkyl which is unsubstituted or substituted by $-N(R^8)_2$, R^8O- or $R^8C(O)NR^8-$.

Preferably, R^{2a} is selected from:H;



Preferably, $R^{2b'}$ and $R^{2b''}$ are independently selected from selected from: H or C_1-C_6 alkyl.

Preferably, R^{3a} and R^{3b} are independently selected from: hydrogen, C_1-C_6 perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m-$, CN, $R^8C(O)-$, $-N(R^8)_2$ and C_1-C_6 alkyl.

Preferably, R^4 is selected from: hydrogen, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m-$, CN, NO_2, $R^8{}_2N-C(NR^8)-$, $R^8C(O)-$, N_3, $-N(R^8)_2$, $R^9OC(O)NR^8-$ and C_1-C_6 alkyl.

Preferably, R^5 is hydrogen or C_1-C_6 alkyl.

Preferably, R^8 is selected from H, C_1-C_6 alkyl and benzyl.

Preferably, A^1 and A^2 are independently selected from: a bond, $-C(O)NR^8-$, $-NR^8C(O)-$, O, $-N(R^8)-$, $-S(O)_2N(R^8)-$ and $-N(R^8)S(O)_2-$.

Preferably, V is selected from hydrogen, heterocycle and aryl.

Preferably, W is imidazolyl.

Preferably, X is a bond or (C=O)-.

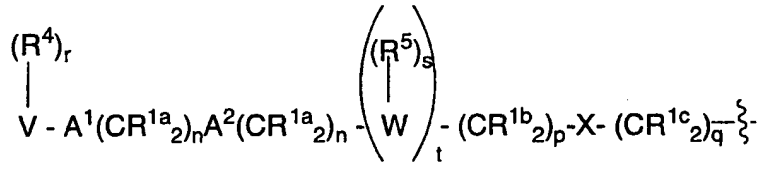
Preferably, n, p and r are independently 0, 1, or 2.

More preferably, r is 1.

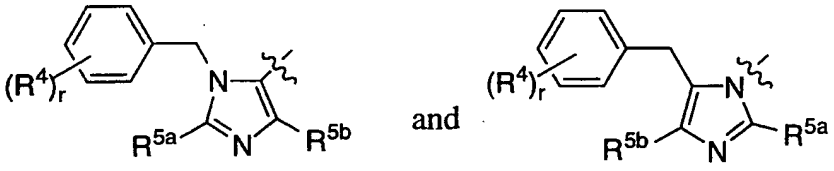
Preferably t is 1.

Preferably u is independently 0 or 1. Most preferably, u is 1.

Preferably, the moiety



is selected from:



The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like: and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

It is intended that the definition of any substituent or variable (e.g., R^{1a}, Z, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, $-N(R^8)_2$ represents $-NH_2$, $-NHCH_3$, $-NHC_2H_5$, etc. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention

which contain a basic moiety by conventional chemical methods. Generally, the salts are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

Abbreviations used in the description of the chemistry and in the Examples that follow are:

Ac_2O	Acetic anhydride;
Boc	t-Butoxycarbonyl;
CBz	Carbobenzyloxy;
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene;
DMAP	4-Dimethylaminopyridine;
DME	1,2-Dimethoxyethane;
DMF	Dimethylformamide;
EDC	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide-hydrochloride;
Et_3N	Triethylamine;
EtOAc	Ethyl acetate;
FAB	Fast atom bombardment;
HOBT	1-Hydroxybenzotriazole hydrate;
HOOBT	3-Hydroxy-1,2,2-benzotriazin-4(3*H*)-one;
HPLC	High-performance liquid chromatography;
MCPBA	m-Chloroperoxybenzoic acid;
MsCl	Methanesulfonyl chloride;
NaHMDS	Sodium bis(trimethylsilyl)amide;
Py	Pyridine;
TFA	Trifluoroacetic acid;
THF	Tetrahydrofuran.

The compounds of this invention are prepared by employing reactions as shown in the Schemes 1-16, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. While stereochemistry is shown in the Schemes, a person of ordinary skill in the art would understand that the illustrated compounds represent racemic mixtures which may be separated at a subsequent purification step or may be utilized as the racemic mixture.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the reductive alkylation or acylation reactions described in the Schemes.

Synopsis of Schemes 1-7:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. For example, see M. Cain *et al.,Heterocycles*, 19:1003 (1982), V. Schollkopf *et al., Angew. Chem. Int. Ed. Engl.,* 26:143(1987), Huber and Seebach, *Helvitica Chim. Acta*, 70:1944 (1987), and J.L. Stanton *et al., J. Med. Chem.,* 26:1267 (1983).

In Schemes 1-2, for example, the syntheses of 1,2,3,4-tetrahydroisoquinoline intermediates are outlined. The subsequent reactions described in the remaining schemes may be similarly applied to suitably protected commercially available tetrahydroisoquinolines, as well as commercially or synthetically obtained homologs, to provide compounds of the instant invention.

Scheme 1 illustrates the synthesis of 1,2,3,4-tetrahydroisoquinolines essentially according to the method of Stokker in *Tetrahedron Letts.*, **1996**, *37*, 5453. Thus, phenethylamines such as **1** may be converted to the corresponding trifluoroacetate **2** using, for example, trifluoroacetic anhydride and an organic base such as triethylamine in a suitable solvent such as dichloromethane. Compound **2** can then be cyclized to **3** using paraformaldehyde in a strong acid

milieu, for example a mixture of acetic acid and concentrated sulfuric acid. Hydrolysis of **3** using aqueous base then affords of 1,2,3,4-tetrahydroisoquinolines such as **4**.

An alternative route to 1,2,3,4-tetrahydroisoquinolines such as **9** is shown in Scheme 2. This is as described by Larsen et al in *J. Org. Chem.*, **1991**, *56*, 6034. Amides such as **5** (obtained by standard coupling of the appropriate phenethylamine and an acid or acid derivative) may be treated with oxalyl chloride in dichloromethane to yield **6** which is then cyclized using a Lewis acid (e.g. $FeCl_3$) to give the intermediate **7**. Treatment of **7** with an acid such as sulfuric acid in a polar solvent (for example methanol) results in the formation of the 3,4-dihydroisoquinoline **8**. Compound **8** may also be obtained from **5** using the well-known Bischler-Napieralski reaction. Reduction of the imine of **8** to **9** may be done with a reducing agent such as sodium borohydride in an alcoholic solvent (e.g. methanol) or, alternatively, asymmetric hydrogenation processes may be employed to give **9** in optically enriched form. Intermediate **9** may be coupled with a suitably substituted acid using standard amide bond formation methods to yield the instant compound **10**.

Scheme 3 illustrates reactions wherein the preferred 4-cyanobenzylimidazolyl moiety is incorporated into the instant compounds.

Schemes 4-5 illustrate the syntheses of 1,2,3,4-tetrahydroisoquinolines of the instant invention wherein the "X" moiety is other than an alkyl bridge. The reactions illustrated therein show the incorporation of sidechains which comprise the preferred 4-cyanobenzylimidazolyl moiety. It is understood that a person of ordinary skill in the art could readily modify such reaction sequences by using appropriate protecting groups and reagents well known to one skilled in the art to provide other compounds of the instant invention.

Scheme 4 illustrates the syntheses of compounds of the instant invention wherein "X" is -S-. Thus the intermediate aldehyde **11** is reduced to the alcohol **12**, activated and treated with a suitable thioacetate to provide the thioester **13**. The thiol is then generated and

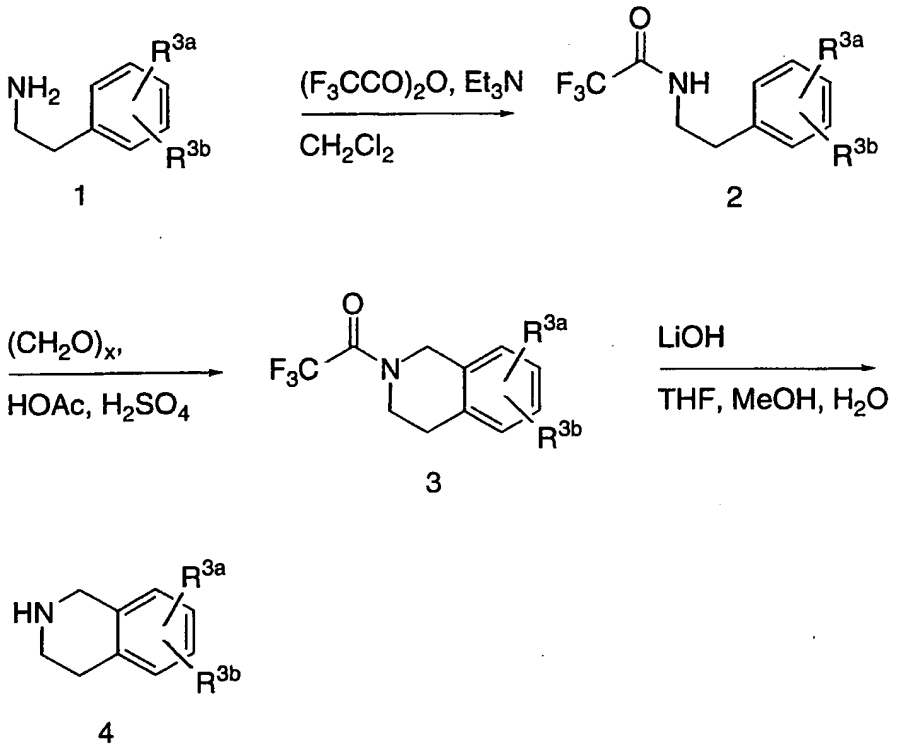
alkylated with a suitable ester containing reagent, such as bromoacetic acid to provide intermediate **14**. Reduction of the ester moiety, followed by oxidation provides the corresponding aldehyde, which can be utilized to reductively alkylate the suitably substituted 1,2,3,4-tetrahydroisoquinoline to provide the instant compound **15**.

Scheme 5 illustrates the syntheses of compounds of the instant invention wherein "X" is -O-. Thus, a dihydroxyalkane, such as ethylene glycol, can be selectively protected and oxidized to provide the aldehyde **16**. Intermediate **16** can be utilized to reductively alkylate the suitably substituted 1,2,3,4-tetrahydroisoquinoline and the sidechain deprotected. Intermediate **17** can then be alkylated with a suitable reagent to provide the instant compound **18** which incorporates the ether moiety.

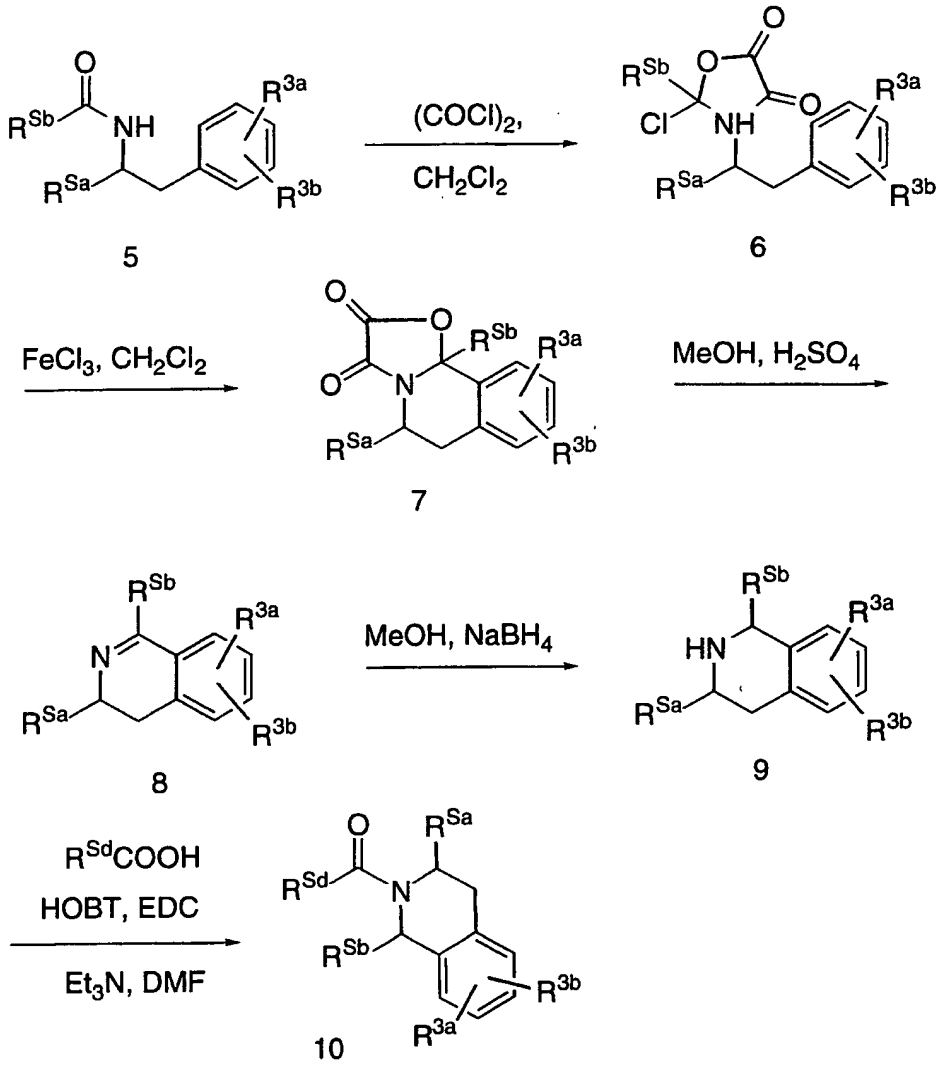
The reagent utilized in the reductive alkylation of the 1,2,3,4-tetrahydroisoquinoline may alternatively incorporate a leaving group which may subsequently react with a blocked imidazolyl reagent, such as **19** to provide compounds of the instant invention wherein "X" is a bond and the preferred imidazolyl is attached to the alkyl bridge via one of the ring nitrogens, as shown in Scheme 6.

Scheme 7 illustrates the syntheses of compounds of the instant invention comprising 3,4-dihydro-1(1H)-isoquinolinones, indoles and benzoimidazoles. Syntheses of suitably substituted indole starting materials are well known in the art and are described in "Comprehensive Heterocyclic Chemistry - Vol. 4", Chapter 3.06: Pyrroles and their Benzo Derivatives: (iii) Synthesis and Applications, R. J. Sundberg.

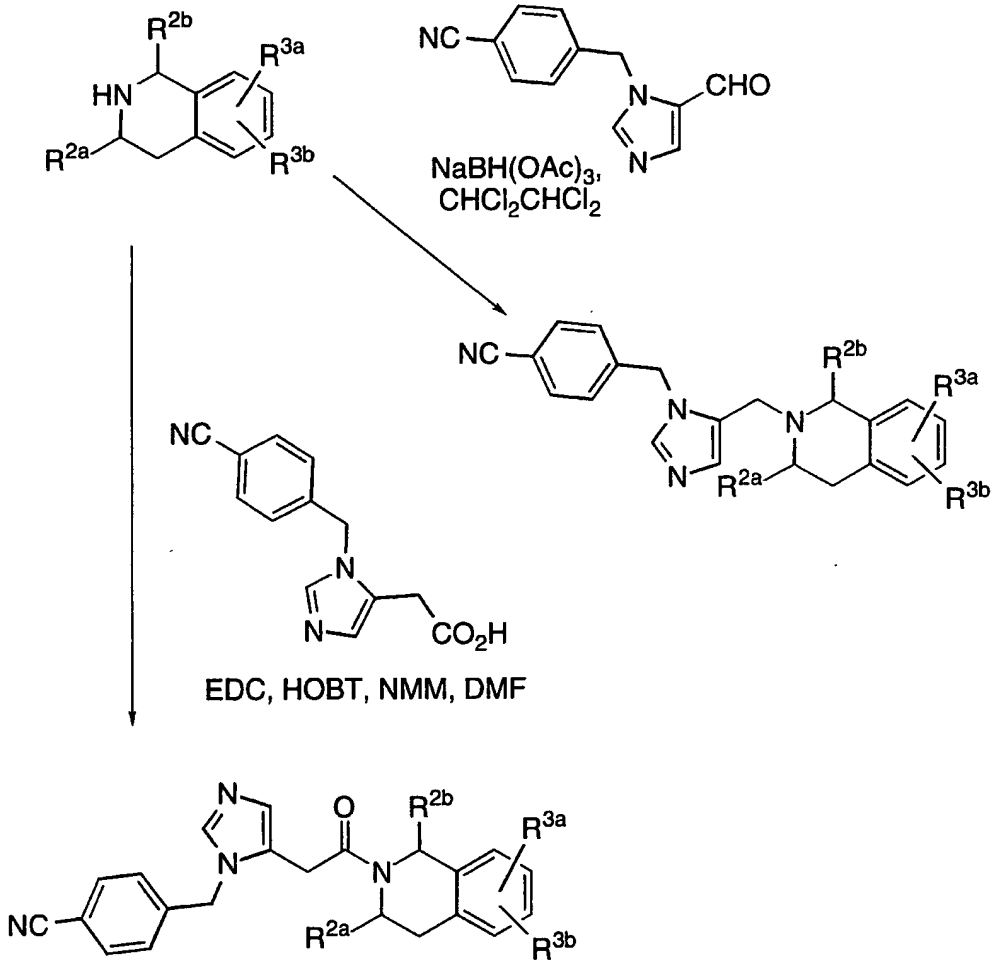
SCHEME 1


NH2
R3a
R3b
1
(F3CCO)2O, Et3N
CH2Cl2
O
F3C
NH
2
(CH2O)x,
HOAc, H2SO4
F3C
N
3
LiOH
THF, MeOH, H2O
HN
4

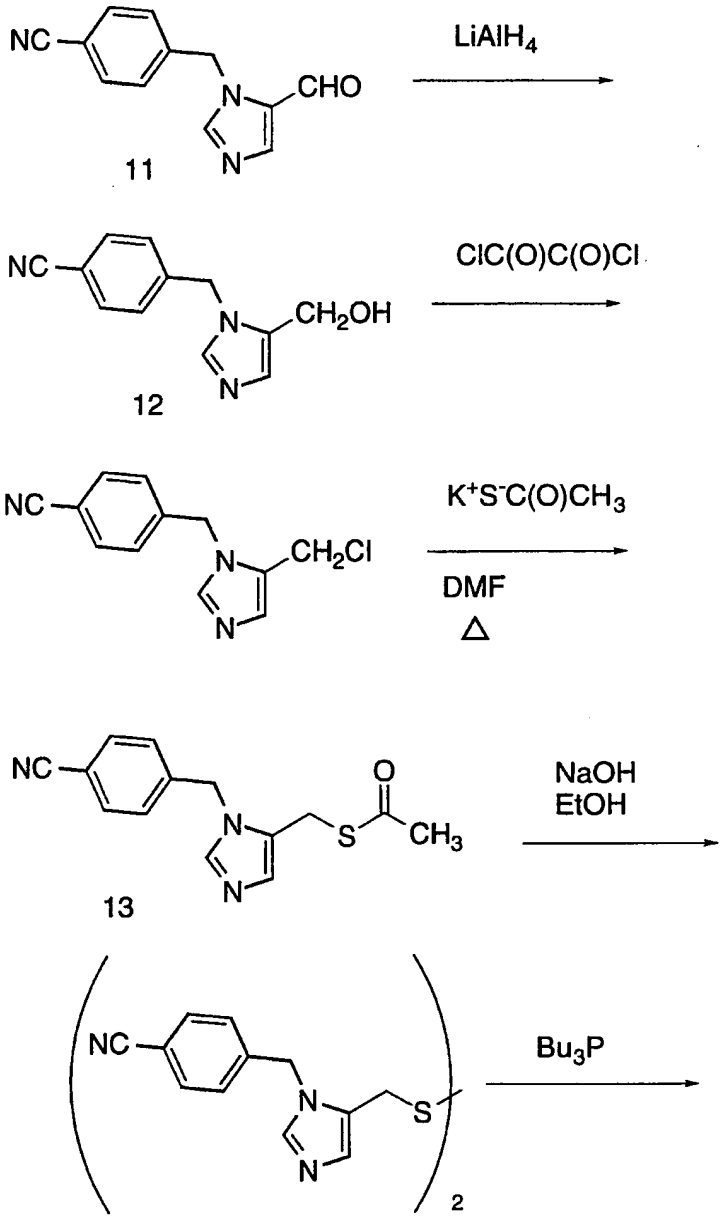
SCHEME 2


R^{Sb}
NH
R^{Sa}
R^{3a}
R^{3b}
5
$(COCl)_2$,
CH_2Cl_2
O
Cl
6
$FeCl_3$, CH_2Cl_2
7
MeOH, H_2SO_4
8
MeOH, $NaBH_4$
HN
9
$R^{Sd}COOH$
HOBT, EDC
Et_3N, DMF
R^{Sd}
10

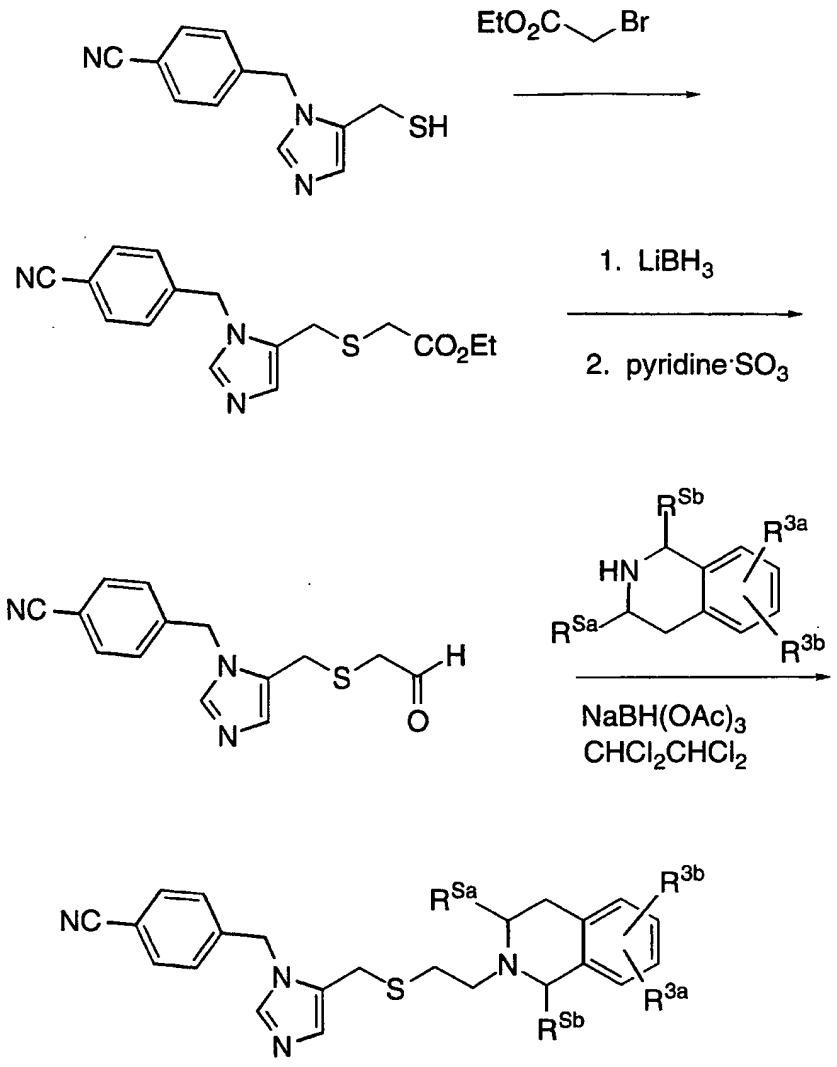
SCHEME 3


R2b
R3a
HN
R2a
R3b
NC
CHO
N
N
NaBH(OAc)3,
CHCl2CHCl2
NC
R2b
R3a
N
N
N
R2a
R3b
NC
N
N
CO2H
EDC, HOBT, NMM, DMF
N
O
R2b
R3a
N
N
NC
R2a
R3b

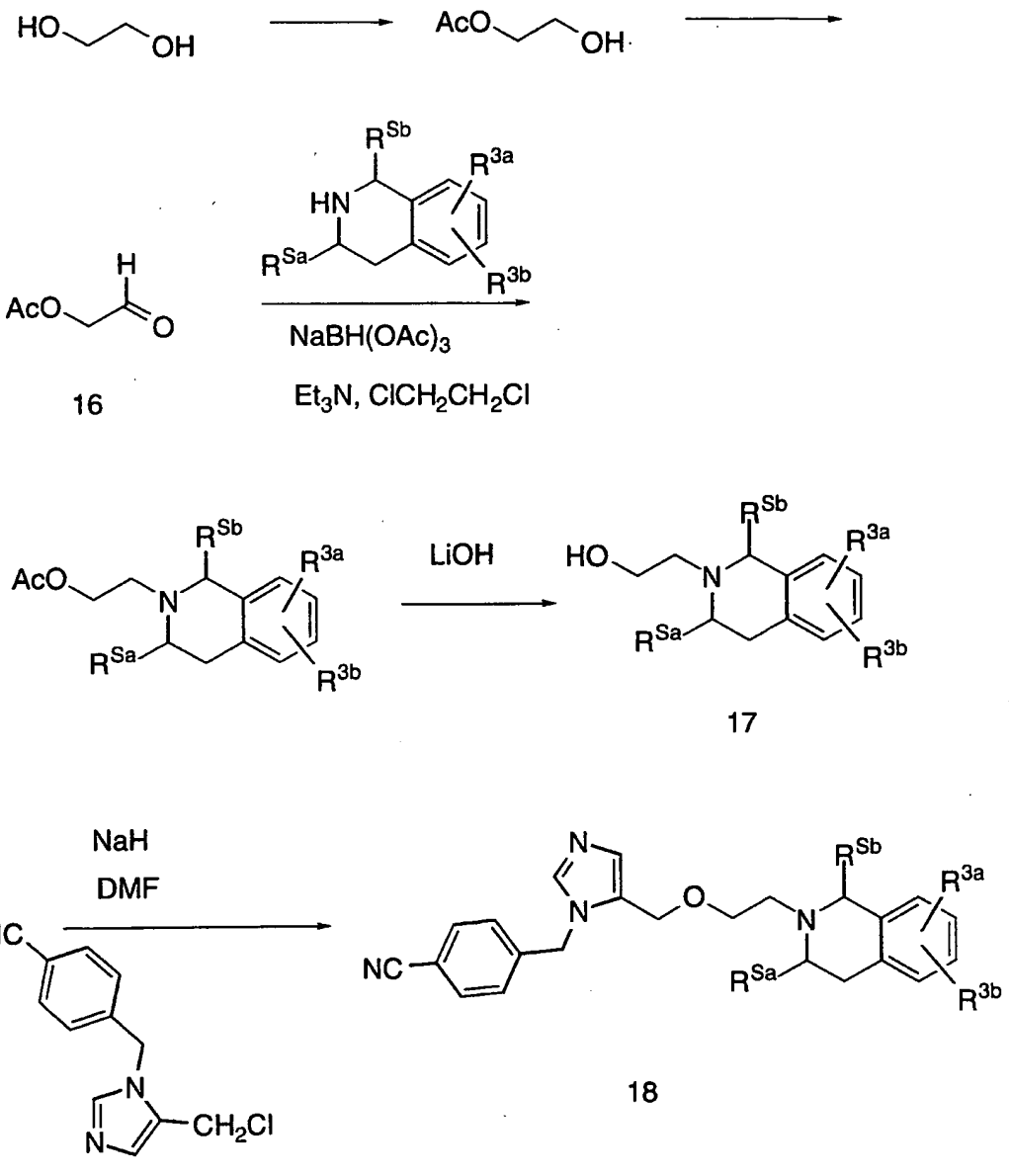
SCHEME 4


NC
CHO
N
N
11
$LiAlH_4$
NC
CH_2OH
12
ClC(O)C(O)Cl
NC
CH_2Cl
$K^+S^-C(O)CH_3$
DMF
Δ
NC
O
S
CH_3
13
NaOH
EtOH
NC
S
2
Bu_3P

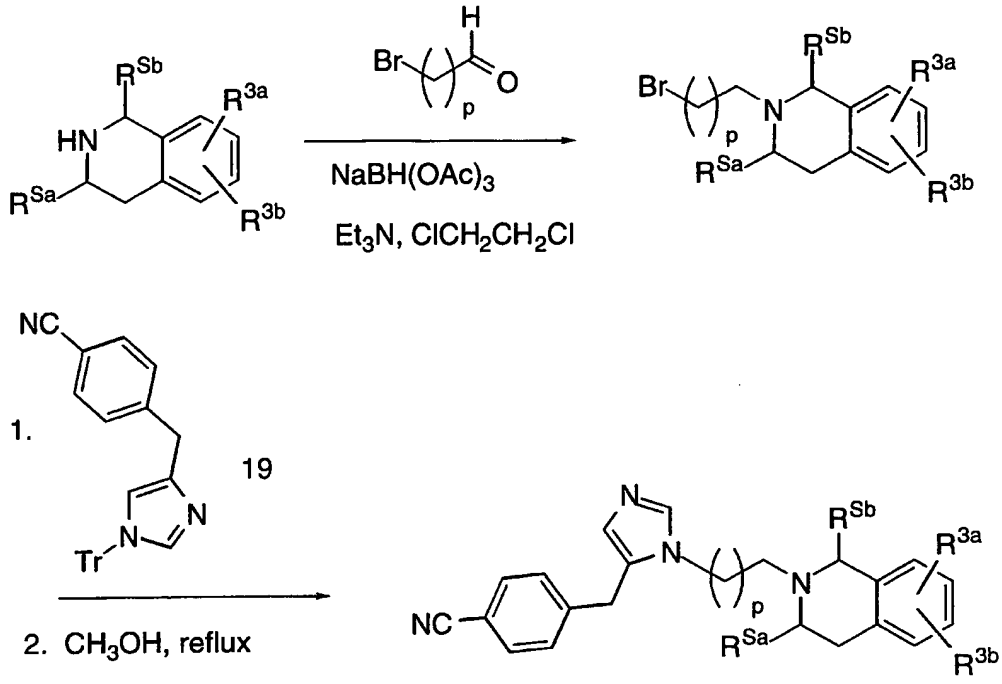
SCHEME 4 (continued)



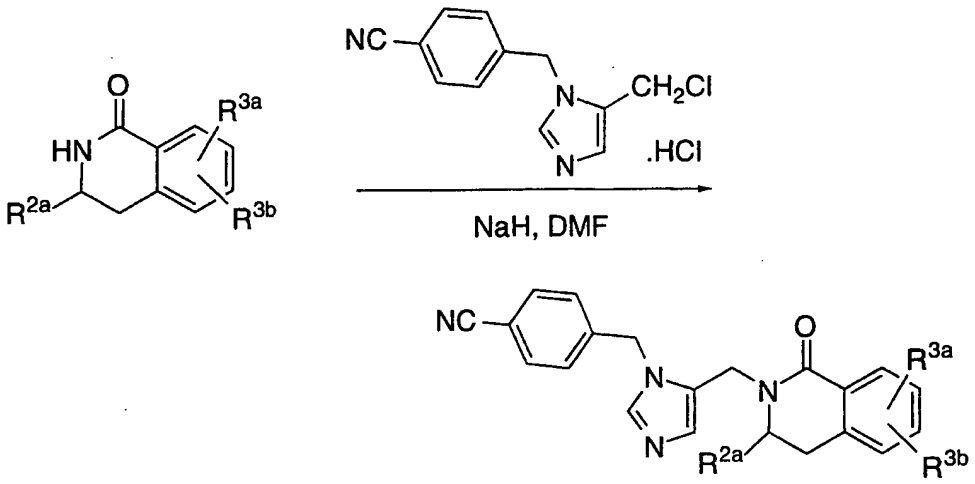
SCHEME 5

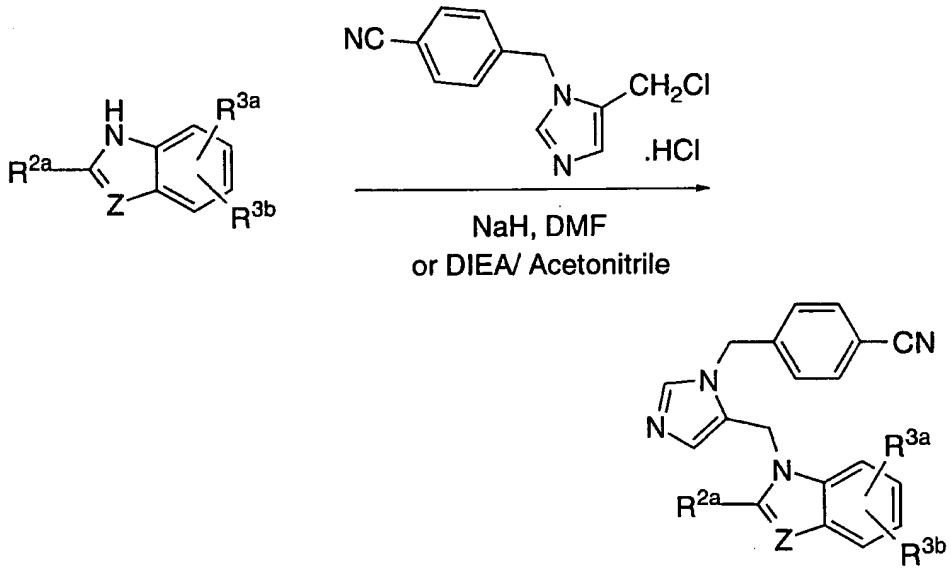

HO
OH
AcO
OH
AcO
H
O
16
R^Sb
R^3a
HN
R^Sa
R^3b
NaBH(OAc)3
Et3N, ClCH2CH2Cl
AcO
N
R^Sa
R^Sb
R^3a
R^3b
LiOH
HO
17
NaH
DMF
NC
N
CH2Cl
18

SCHEME 6

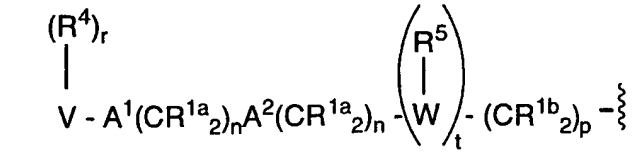

R^Sb
R^3a
HN
R^Sa
R^3b
H
Br
O
p
NaBH(OAc)3
Et3N, ClCH2CH2Cl
Br
N
p
R^Sa
R^Sb
R^3a
R^3b
NC
1.
19
N
N
Tr
2. CH3OH, reflux
NC
N
N
p
R^Sb
R^3a
R^Sa
R^3b

SCHEME 7


NC
CH2Cl
.HCl
NaH, DMF
HN
O
R3a
R2a
R3b
N
N


NC
CH2Cl
.HCl
NaH, DMF
or DIEA/ Acetonitrile
H
N
Z
R2a
R3a
R3b
CN

In the above Schemes it is understood that

R^{Sd} is 

or a protected precursor thereof;

R^{Sa}- is R^{2a} or a protected precusor thereof; and
R^{Sb}- is $R^{2b'}$, $R^{2b''}$ or a protected precusor thereof; and
R- is a "substituent" or a protected precusor thereof.

It is understood that a variety of amines and acids, either commercially available or readily synthesized by reactions well known in the art, which contain the side-chain moieties R^{Sa} and $R^{Sd}(C=O)$ may be utilized in the reactions described hereinabove. Schemes 8-16 illustrate specific reactions wherein such intermediates containing the side-chain moieties R^{Sa} and $R^{Sd}(C=O)$ may be prepared. It is understood that while Schemes 8-16 illustrate preparation of both protected and unprotected intermediates, a person of ordinary skill would appreciate that subsequent reactions which utilize those intermediates, such as those described in Schemes 1-7, may require protection and eventual deprotection of certain intermediate moieties.

The selectively protected intermediate **20** utilized in the synthesis illustrated in Scheme 8 can be reductively alkylated with a variety of aldehydes, such as **21**. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, 1988, *67*, 69-75. The reductive alkylation can be accomplished at pH 5-7 with a variety of reducing agents, such as sodium triacetoxyborohydride or sodium cyanoborohydride in a solvent such as dichloroethane, methanol or dimethylformamide. The ester product **22** can be deprotected with trifluoroacetic acid in methylene chloride to give the substituted diamine **23**. That diamine may be isolated in the salt form, for example, as a

trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine **23** can be further selectively protected and reductively alkylated with a second aldehyde to obtain an analogous tertiary amine. Alternatively, the diamine **23** can be cyclized to obtain intermediates such as the dihydroimidazole **24** by procedures known in the literature. The ester **24** can then be utilized in a reaction such as illustrated in Scheme 3 hereinabove.

Scheme 9 illustrates a general preparation of aralkyl imidazolyl intermediates **31** that can be utilized in reactions such as illustrated in Scheme 3. Thus imidazole acetic acid **27** can be converted to the protected acetate **29** by standard procedures, and **29** can be first reacted with an alkyl halide, then treated with refluxing methanol to provide the regiospecifically alkylated imidazole acetic acid ester **30**. Hydrolysis provides the acetic acid **31**.

Schemes 10-13 illustrate syntheses of suitably substituted alkanols useful in the syntheses of the instant compounds wherein the variable W is present as a pyridyl moiety. The hydroxyl moiety of such intermediates may be converted into the corresponding aldehyde, as illustrated in Scheme 10 or may be converted to a suitable leaving group, as illustrated in Scheme 12. Similar synthetic strategies for preparing alkanols that incorporate other heterocyclic moieties for variable W are also well known in the art.

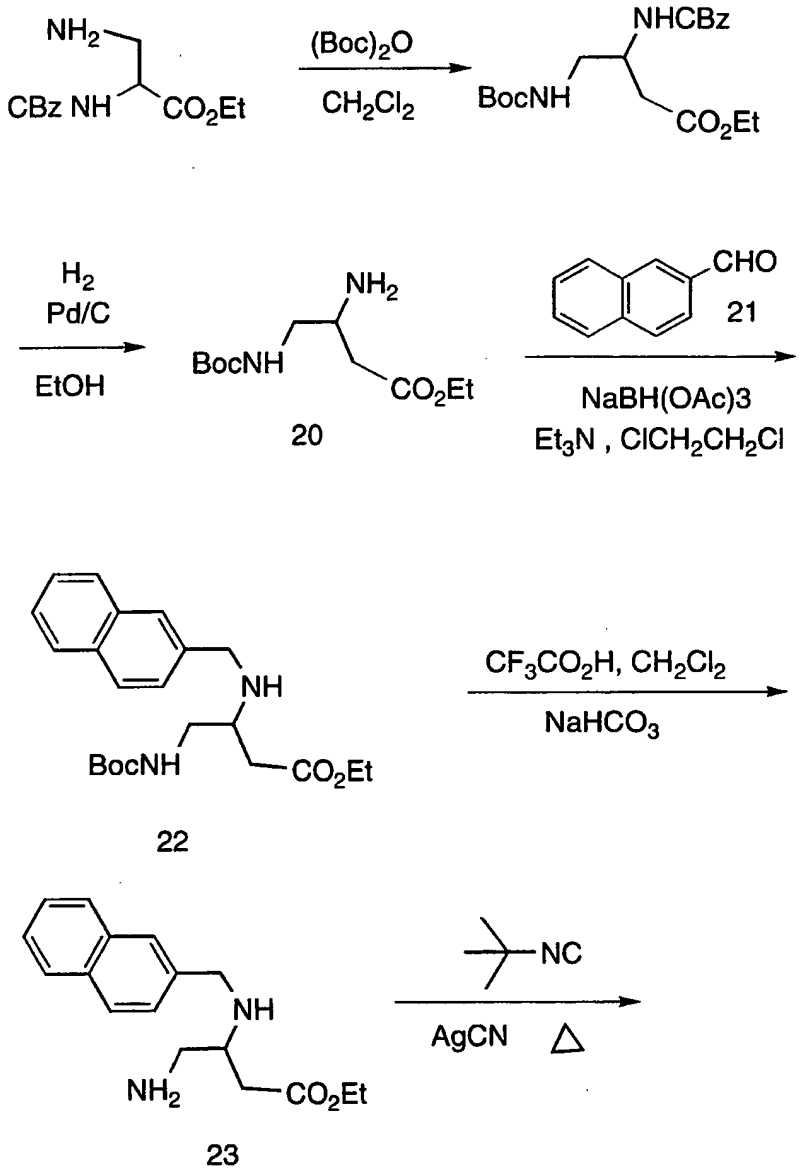
Compounds of the instant invention wherein the $A^1(CR^{1a}{}_2)_nA^2(CR^{1a}{}_2)_n$ linker is a substituted methylene may be synthesized by the methods shown in Scheme 14. Thus, the N-protected imidazolyl iodide **32** is reacted, under Grignard conditions with a suitably protected benzaldehyde to provide the alcohol **33**. Acylation, followed by the alkylation procedure illustrated in the Schemes above (in particular, Scheme 6) provides the instant compound **34**. If other R^1 substituents are desired, the acetyl moiety can be manipulated as illustrated in the Scheme.

Scheme 15 illustrates synthesis of an instant compound wherein a non-hydrogen R^{5b} is incorporated in the instant compound. Thus, a readily available 4-substituted imidazole **37** may be selectively

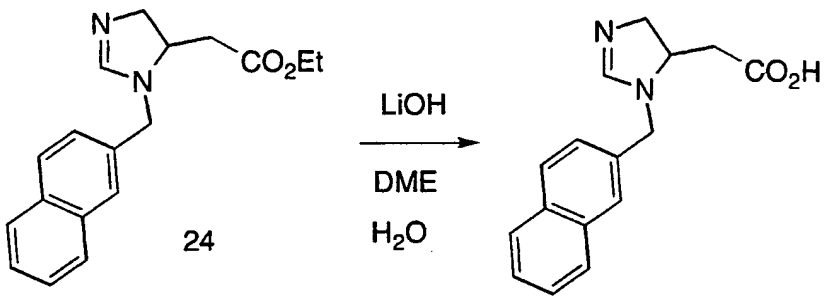
iodinated to provide the 5-iodoimidazole **38**. That imidazole may then be protected and coupled to a suitably substituted benzyl moiety to provide intermediate **39**. Intermediate **39** can then undergo the alkylation reactions that were described hereinabove.

Compounds of the instant invention wherein the $A^1(CR^{1a}{}_2)_nA^2(CR^{1a}{}_2)_n$ linker is oxygen may be synthesized by methods known in the art, for example as shown in Scheme 16. The suitably substituted phenol **41** may be reacted with methyl N-(cyano)methanimidate to provide the 4-phenoxyimidazole **42**. After selective protection of one of the imidazolyl nitrogens, the intermediate **43** can undergo alkylation reactions as described for the benzylimidazoles hereinabove.

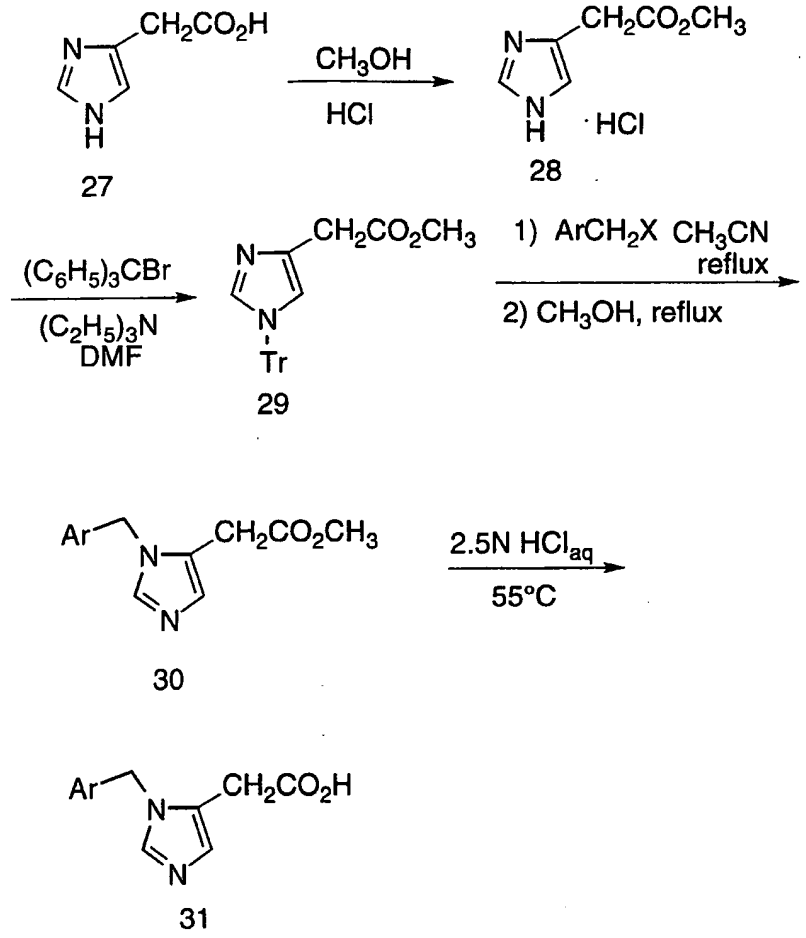
SCHEME 8


NH2
CBz NH
CO2Et
(Boc)2O
CH2Cl2
NHCBz
BocNH
CO2Et
H2
Pd/C
EtOH
NH2
BocNH
CO2Et
20
CHO
21
NaBH(OAc)3
Et3N , ClCH2CH2Cl
NH
BocNH
CO2Et
22
CF3CO2H, CH2Cl2
NaHCO3
NC
AgCN
NH
NH2
CO2Et
23

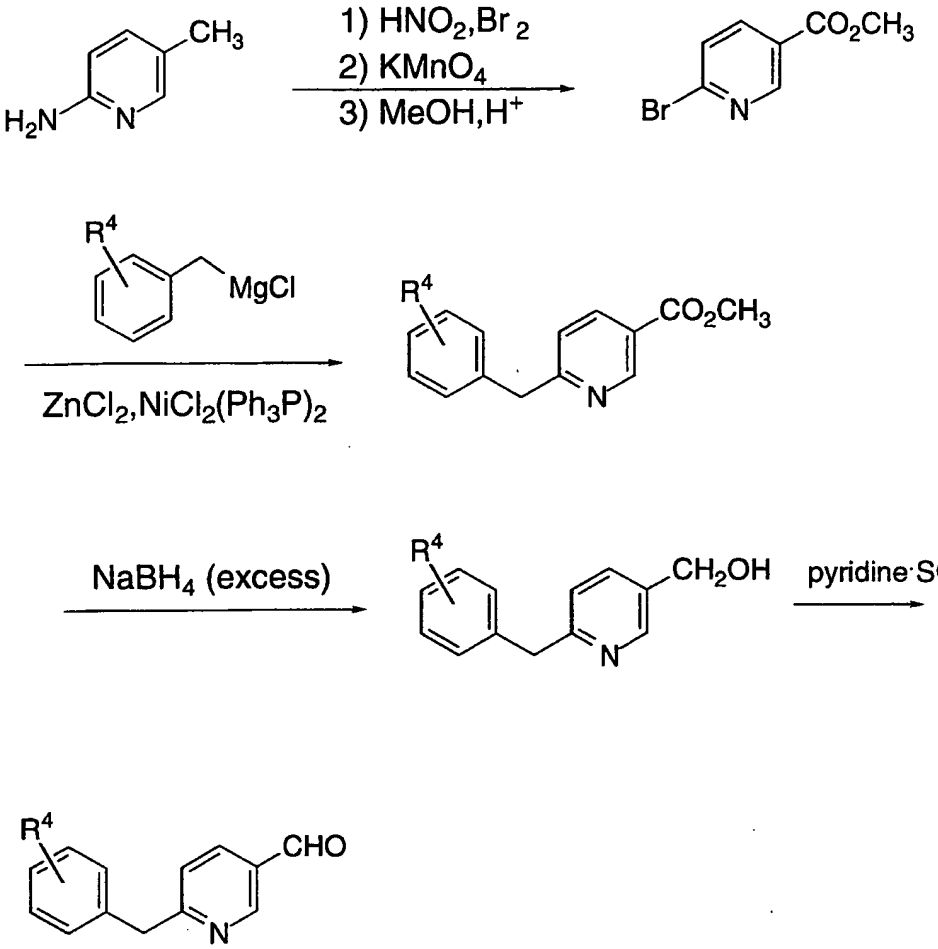
SCHEME 8 (continued)



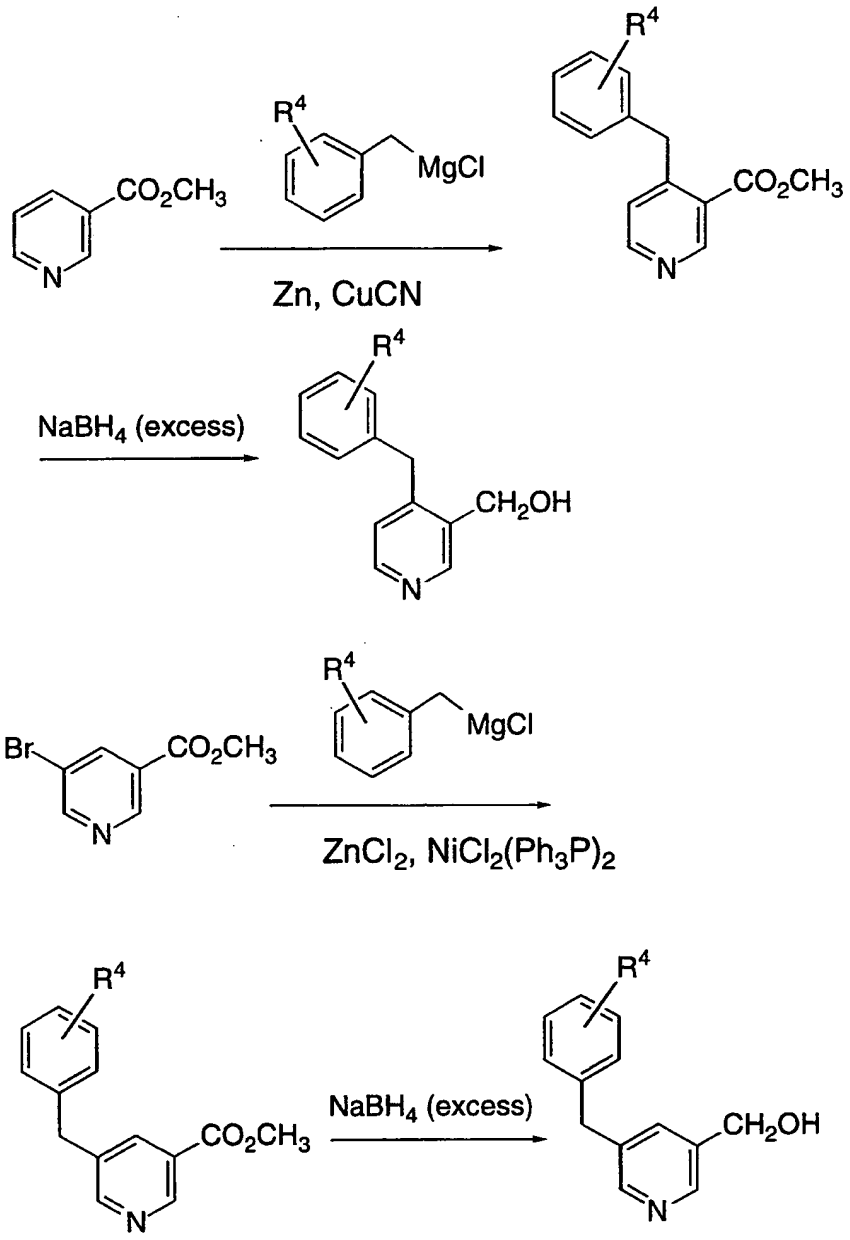
SCHEME 9


CH2CO2H
N
N
H
27
CH3OH
HCl
CH2CO2CH3
N
N
H
·HCl
28
(C6H5)3CBr
(C2H5)3N
DMF
CH2CO2CH3
N
N
Tr
29
1) ArCH2X CH3CN
reflux
2) CH3OH, reflux
Ar
N
N
CH2CO2CH3
30
2.5N HClaq
55°C
Ar
N
N
CH2CO2H
31

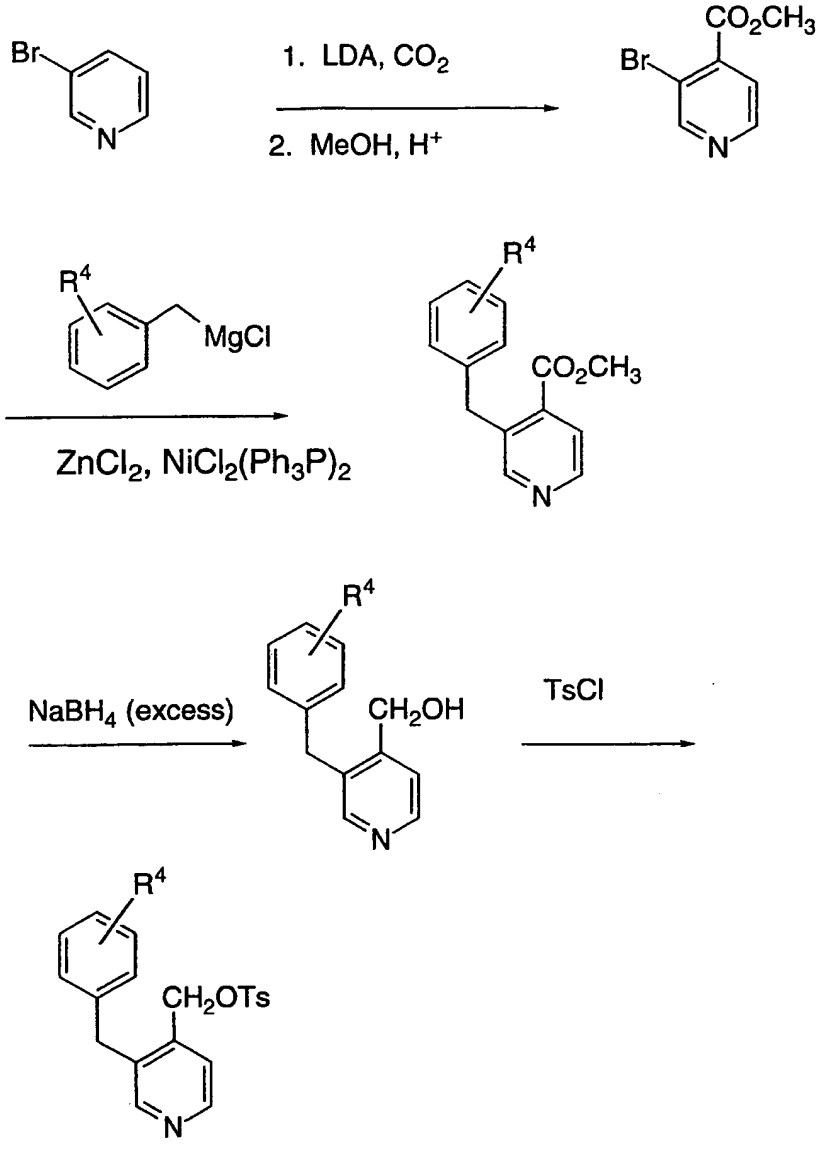
SCHEME 10


CH3
H2N
N
1) HNO2,Br 2
2) KMnO4
3) MeOH,H+
CO2CH3
Br
N
R4
MgCl
ZnCl2,NiCl2(Ph3P)2
R4
CO2CH3
N
NaBH4 (excess)
R4
CH2OH
N
pyridine·SO3
R4
CHO
N

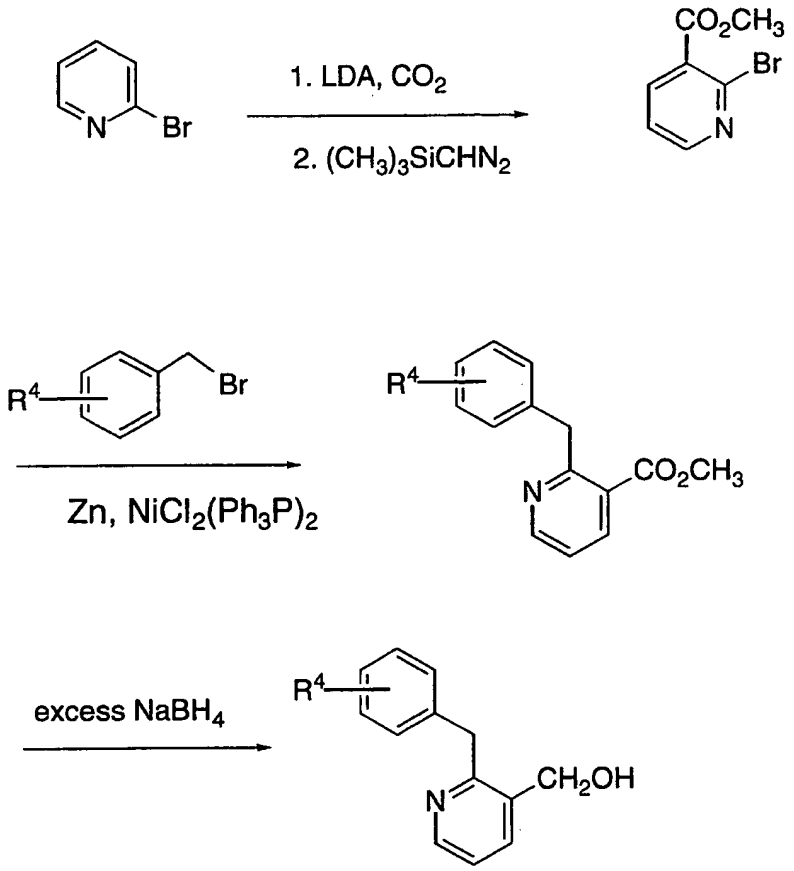
SCHEME 11


R4
MgCl
CO2CH3
N
Zn, CuCN
NaBH4 (excess)
CH2OH
Br
ZnCl2, NiCl2(Ph3P)2

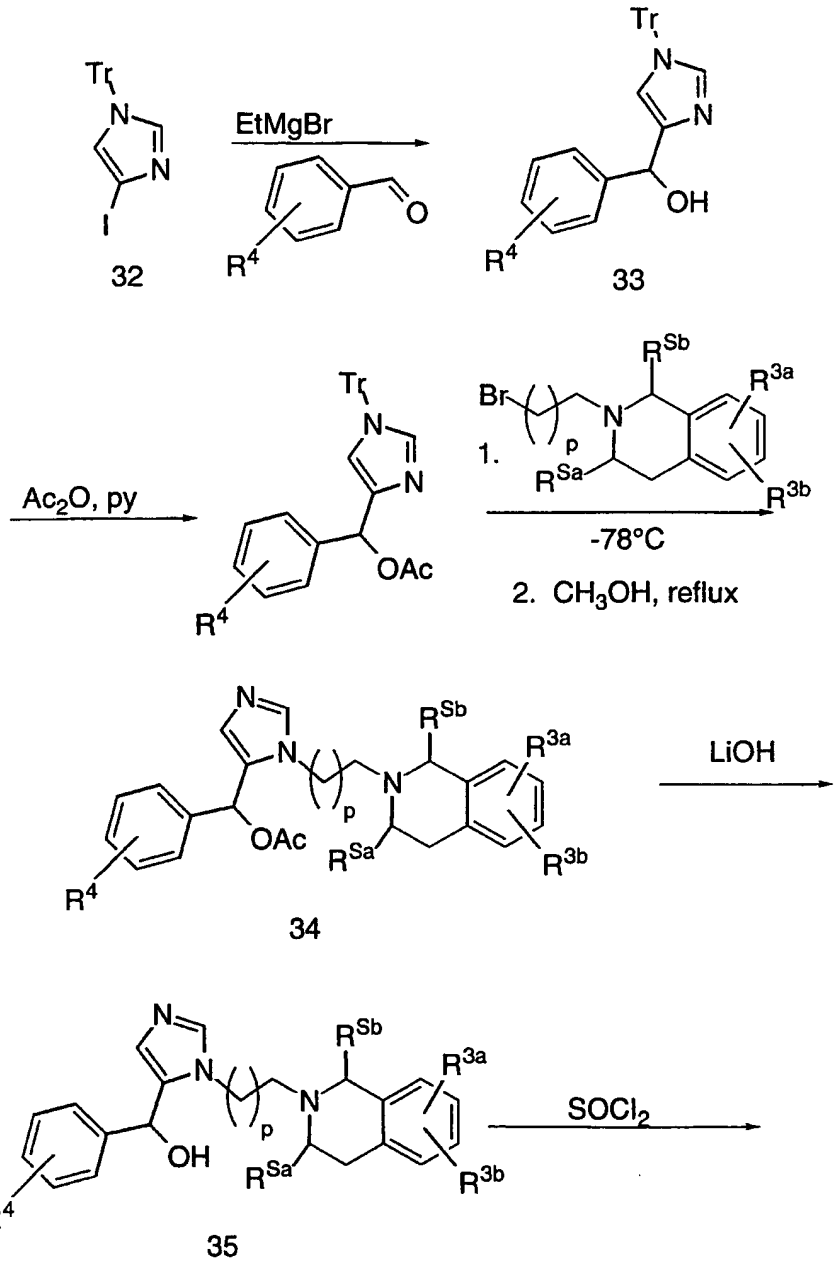
SCHEME 12


Br
N
1. LDA, CO_2
2. MeOH, H^+
CO_2CH_3
Br
N
R^4
MgCl
$ZnCl_2$, $NiCl_2(Ph_3P)_2$
R^4
CO_2CH_3
N
$NaBH_4$ (excess)
R^4
CH_2OH
N
TsCl
R^4
CH_2OTs
N

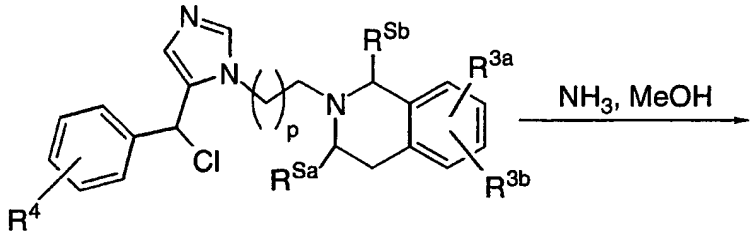
SCHEME 13


1. LDA, CO_2
2. $(CH_3)_3SiCHN_2$
CO_2CH_3
Br
N
R^4
Br
Zn, $NiCl_2(Ph_3P)_2$
excess $NaBH_4$
CH_2OH

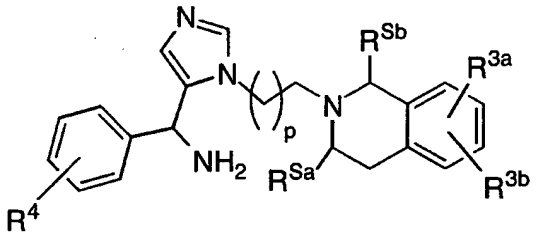
SCHEME 14


Tr
N
N
I
32
EtMgBr
O
R4
OH
33
Ac2O, py
OAc
Br
p
1.
RSa
RSb
R3a
R3b
-78°C
2. CH3OH, reflux
34
LiOH
SOCl2
35

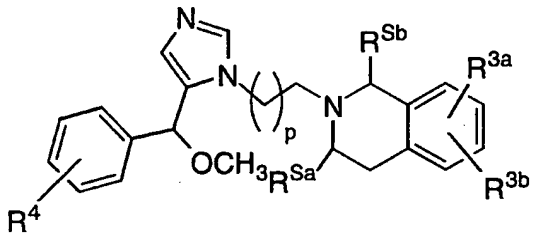
SCHEME 14 (continued)



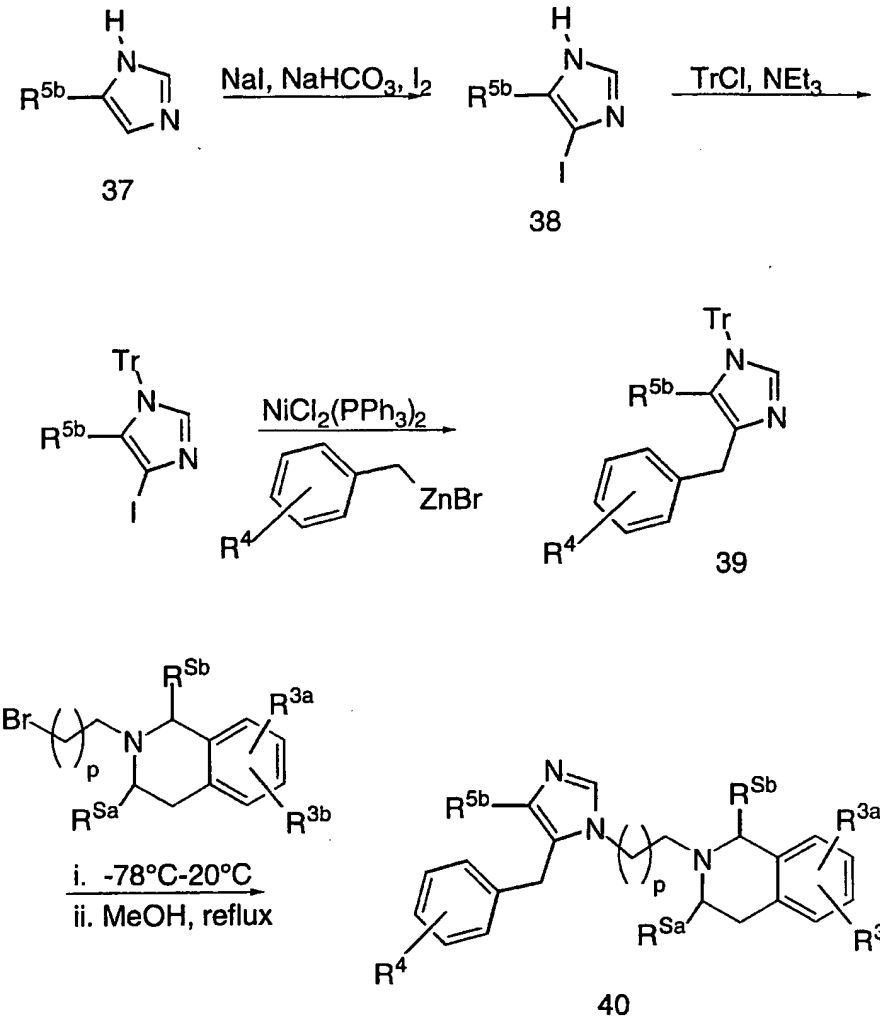
36



+

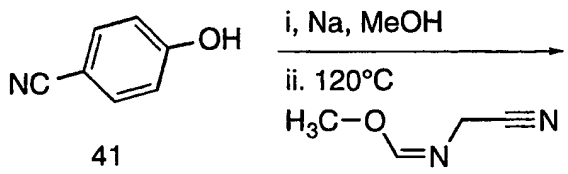


SCHEME 15

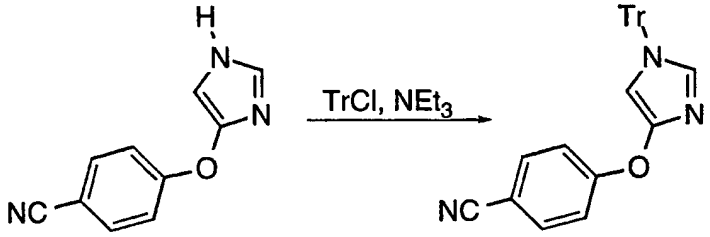


37 38 39 40

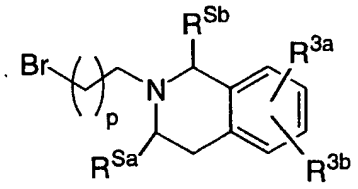
SCHEME 16



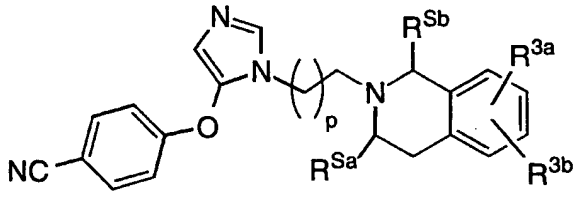
41



42 43



i. -78°C-20°C
ii. MeOH reflux



The instant compounds are useful as pharmaceutical agents for mammals, especially for humans. These compounds may be administered to patients for use in the treatment of cancer. Examples of the type of cancer which may be treated with the compounds of this invention include, but are not limited to, colorectal carcinoma, exocrine pancreatic carcinoma, myeloid leukemias and neurological tumors. Such tumors may arise by mutations in the *ras* genes themselves, mutations in the proteins that can regulate Ras activity (i.e., neurofibromin (NF-1), neu, scr, abl, lck, fyn) or by other mechanisms.

The compounds of the instant invention inhibit farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. The instant compounds may also inhibit tumor angiogenesis, thereby affecting the growth of tumors (J. Rak et al. *Cancer Research*, 55:4575-4580 (1995)). Such anti-angiogenesis properties of the instant compounds may also be useful in the treatment of certain forms of blindness related to retinal vascularization.

The compounds of this invention are also useful for inhibiting other proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes (i.e., the Ras gene itself is not activated by mutation to an oncogenic form) with said inhibition being accomplished by the administration of an effective amount of the compounds of the invention to a mammal in need of such treatment. For example, the compounds are useful in the treatment of neurofibromatosis, which is a benign proliferative disorder.

The instant compounds may also be useful in the treatment of certain viral infections, in particular in the treatment of hepatitis delta and related viruses (J.S. Glenn et al. *Science*, 256:1331-1333 (1992).

The compounds of the instant invention are also useful in the prevention of restenosis after percutaneous transluminal coronary angioplasty by inhibiting neointimal formation (C. Indolfi et al. *Nature medicine*, 1:541-545(1995).

The instant compounds may also be useful in the treatment and prevention of polycystic kidney disease (D.L. Schaffner et al. *American Journal of Pathology*, 142:1051-1060 (1993) and B. Cowley, Jr. et al.*FASEB Journal*, 2:A3160 (1988)).

The instant compounds may also be useful for the treatment of fungal infections.

In a preferred embodiment of the instant invention the compounds of this instant invention are selective inhibitors of farnesyl-protein transferase. A compound is considered a selective inhibitor of farnesyl-protein transferase, for example, when its *in vitro* farnesyl-protein transferase inhibitory activity, as assessed by the assay described in Example 41, is at least 100 times greater than the *in vitro* activity of the same compound against geranylgeranyl-protein transferase-type I in the assay described in Example 42. Preferably, a selective compound exhibits at least 1000 times greater activity against one of the enzymatic activities when comparing geranylgeranyl-protein transferase-type I inhibition and farnesyl-protein transferase inhibition.

In another preferred embodiment of the instant invention the compounds of this instant invention are dual inhibitors of farnesyl-protein transferase and geranylgeranyl-protein transferase type I. Such a dual inhibitor will exhibit certain characteristics when assessed in *in vitro* assays, which are dependent on the type of assay employed.

In a SEAP assay, such as described in Example 45, it is preferred that the dual inhibitor compound has an *in vitro* inhibitory activity (IC_{50}) that is less than about 12μM against K4B-Ras dependent activation of MAP kinases in cells. More preferably, the dual inhibitor compound has an *in vitro* inhibitory activity (IC_{50}) against K4B-Ras dependent activation of MAP kinases in cells which is more than about 5 times lower than the inhibitory activity (IC_{50}) against Myr-Ras dependent activation of MAP kinases in cells. Also more preferably, in a SEAP assay, the dual inhibitor compound has an inhibitory activity (IC_{50}) that is less than about 10 nM against H-Ras dependent activation of MAP kinases in cells.

In a GGTase plus anion assay, such as described in Example 42, it is preferred that the dual inhibitor compound has an *in vitro* inhibitory activity (IC_{50}) that is less than about 5 μM against transfer of a geranylgeranyl residue to a protein or peptide substrate comprising a $CAAX^G$ motif by geranylgeranyl-protein transferase type I in the presence of a modulating anion. More preferably, the dual inhibitor compound has an *in vitro* inhibitory activity (IC_{50}) that is less than about 1 μM against transfer of a geranylgeranyl residue to a protein or peptide substrate comprising a $CAAX^G$ motif by geranylgeranyl-protein transferase type I in the presence of a modulating anion. Preferably, the dual inhibitor compound has an *in vitro* inhibitory activity (IC_{50}) in the in vitro assay as described in Example 41 that is less than about 1 μM against transfer of a farnesyl residue to a protein or peptide substrate, comprising a $CAAX^F$ motif, by farnesyl-protein transferase. more preferably, the dual inhibitor compound has an *in vitro* inhibitory activity (IC_{50}) that is less than about 100nM against transfer of a farnesyl residue to a protein or peptide substrate, comprising a $CAAX^F$ motif, by farnesyl-protein transferase. Also preferably, the dual inhibitor compound has an *in vitro* inhibitory activity (IC_{50}) in the in vitro assay as described in Example 44, that is less than about 100 nM against the anchorage independent growth of H-*ras*-transformed mammalian fibroblasts.

The protein or peptide substrate utilized in the instant assay may incorporate any CAAX motif that is geranylgeranylated by GGTase-I. The term "$CAAX^G$," will refer to such motifs that may be geranylgeranylated by GGTase-I. It is understood that some of the "$CAAX^G$," containing protein or peptide substrates may also be farnesylated by farnesyl-protein transferase. In particular such "$CAAX^G$," motifs include (the corresponding human protein is in parentheses): CVIM (K4B-Ras) (SEQ.ID.NO.: 1), CVLL (mutated H-Ras) (SEQ.ID.NO.: 2), CVVM (N-Ras) (SEQ.ID.NO.: 3), CIIM (K4A-Ras) (SEQ.ID.NO.: 4), CLLL (Rap-IA) (SEQ.ID.NO.: 5), CQLL (Rap-IB) (SEQ.ID.NO.: 6), CSIM

(SEQ.ID.NO.: 7), CAIM (SEQ.ID.NO.: 8), CKVL (SEQ.ID.NO.: 9) and CLIM (PFX) (SEQ.ID.NO.: 10). Preferably, the CAAX motif is CVIM (SEQ.ID.NO.: 1).

As used herein, the term "$CAAX^F$," is used to designate a protein or peptide substrate that incorporates four amino acid C-terminus motif that is farnesylated by farnesyl-protein transferase. It is understood that certain of the "$CAAX^F$," containing protein or peptide substrates may also be geranylgeranylated by GGTase-I. In particular such "$CAAX^F$," motifs include (the corresponding human protein is in parentheses): CVLS (H-ras) (SEQ.ID.NO.: 11), CVIM (K4B-Ras) (SEQ.ID.NO.: 1) and CVVM (N-Ras) (SEQ.ID.NO.: 3).

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

For oral use of a chemotherapeutic compound according to this invention, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For

intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's intramuscular blood-stream by local bolus injection.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specific amounts, as well as any product which results, directly or indirectly, from combination of the specific ingredients in the specified amounts.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The compounds of the instant invention are also useful as a component in an assay to rapidly determine the presence and quantity of farnesyl-protein transferase (FPTase) in a composition. Thus the composition to be tested may be divided and the two portions contacted with mixtures which comprise a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate and, in one of the mixtures, a compound of the instant invention. After the assay mixtures are incubated for an

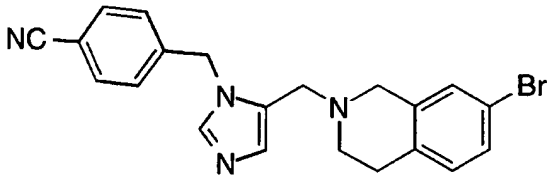
sufficient period of time, well known in the art, to allow the FPTase to farnesylate the substrate, the chemical content of the assay mixtures may be determined by well known immunological, radiochemical or chromatographic techniques. Because the compounds of the instant invention are selective inhibitors of FPTase, absence or quantitative reduction of the amount of substrate in the assay mixture without the compound of the instant invention relative to the presence of the unchanged substrate in the assay containing the instant compound is indicative of the presence of FPTase in the composition to be tested.

It would be readily apparent to one of ordinary skill in the art that such an assay as described above would be useful in identifying tissue samples which contain farnesyl-protein transferase and quantitating the enzyme. Thus, potent inhibitor compounds of the instant invention may be used in an active site titration assay to determine the quantity of enzyme in the sample. A series of samples composed of aliquots of a tissue extract containing an unknown amount of farnesyl-protein transferase, an excess amount of a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate are incubated for an appropriate period of time in the presence of varying concentrations of a compound of the instant invention. The concentration of a sufficiently potent inhibitor (i.e., one that has a Ki substantially smaller than the concentration of enzyme in the assay vessel) required to inhibit the enzymatic activity of the sample by 50% is approximately equal to half of the concentration of the enzyme in that particular sample.

EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof. Purification by HPLC was utilized for Example 1 as set forth below.

EXAMPLE 1



7-Bromo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

Step 1: Preparation of 1-triphenylmethyl-4-(hydroxymethyl)-imidazole

To a solution of 4-(hydroxymethyl)imidazole hydrochloride (35 g) in 250 mL of dry DMF at room temperature was added triethylamine (90.6 mL). A white solid precipitated from the solution. Chlorotriphenylmethane (76.1 g) in 500 mL of DMF was added dropwise. The reaction mixture was stirred for 20 hours, poured over ice, filtered, and washed with ice water. The resulting product was slurried with cold dioxane, filtered, and dried *in vacuo* to provide the title compound as a white solid which was sufficiently pure for use in the next step.

Step 2: Preparation of 1-triphenylmethyl-4-(acetoxymethyl)-imidazole

The alcohol prepared above was suspended in 500 mL of pyridine. Acetic anhydride (74 mL) was added dropwise, and the reaction was stirred for 48 hours during which it became homogeneous. The solution was poured into 2 L of EtOAc, washed with water (3 x 1 L), 5% aq. HCl soln. (2 x 1 L), sat. aq. $NaHCO_3$, and brine, then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product. The title compound was isolated as a white powder which was sufficiently pure for use in the next step.

Step 3: Preparation of 1-(4-cyanobenzyl)-5-(acetoxymethyl)-imidazole hydrobromide

A solution of the acetate from Step 2 (85.8 g) and α-bromo-*p*-tolunitrile (50.1 g) in 500 mL of EtOAc was stirred at 60 °C for 20 hours, during which a pale yellow precipitate formed. The reaction was cooled to room temperature and filtered to provide the solid imidazolium bromide salt. The filtrate was concentrated *in vacuo* to a volume 200 mL, reheated at 60 °C for two hours, cooled to room temperature, and filtered again. The filtrate was concentrated *in vacuo* to a volume 100 mL, reheated at 60 °C for another two hours, cooled to room temperature, and concentrated *in vacuo* to provide a pale yellow solid. All of the solid material was combined, dissolved in 500 mL of methanol, and warmed to 60 °C. After two hours, the solution was reconcentrated *in vacuo* to provide a white solid which was triturated with hexane to remove soluble materials. Removal of residual solvents *in vacuo* provided the titled product hydrobromide as a white solid which was used in the next step without further purification.

Step 4: Preparation of 1-(4-cyanobenzyl)-5-(hydroxymethyl)-imidazole

To a solution of the product from Step 3 (50.4 g) in 1.5 L of 3:1 THF/water at 0 °C was added lithium hydroxide monohydrate (18.9 g). After one hour, the reaction was concentrated *in vacuo*, diluted with EtOAc (3 L), and washed with water, sat. aq. $NaHCO_3$ and brine. The solution was then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product as a pale yellow fluffy solid which was sufficiently pure for use in the next step without further purification.

Step 5: Preparation of 1-(4-cyanobenzyl)-5-imidazole-carboxaldehyde

To a solution of the alcohol from Step 4 (21.5 g) in 500 mL of DMSO at room temperature was added triethylamine (56 mL), then SO_3-pyridine complex (40.5 g). After 45 minutes, the reaction was poured into 2.5 L of EtOAc, washed with water (4 x 1 L) and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the title aldehyde as a white powder which was sufficiently pure for use in the next step without further purification.

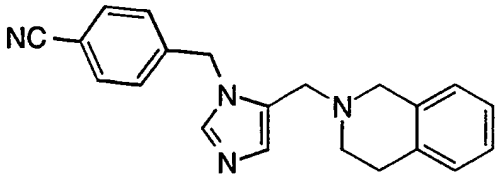
Step 6: Preparation of 7-bromo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

To a solution of 7-bromo-1,2,3,4-tetrahydroisoquinoline (0.742 g, 3.5 mmol) in $CHCl_2CHCl_2$ (15 mL) was added 1-(4-cyanobenzyl)-5-imidazole carboxaldehyde (0.812 g, 3.85 mmol), 4Å sieves and $NaBH(OAc)_3$ (1.11 g, 5.25 mmol). The mixture was stirred at room temperature for 16 h. and a further portion of $NaBH(OAc)_3$ (0.55 g, 2.6 mmol) was added. After an additional 24 h the mixture was diluted with EtOAc, filtered through celite, washed with brine, dried (Na_2SO_4) and concentrated. The residue was stirred in 2N Hcl (50 mL) for 2 h. then extracted with ether. The aqueous layer was basified with 6N KOH and extracted 3X CH_2Cl_2 which was then washed with brine, dried (Na_2SO_4) and the solvent evaporated in vacuo. Crystallization from ether afforded the title compound as a white solid.

Analysis for $C_{21}H_{19}N_4Br$

Calcd.	C, 61.92; H, 4.70; N,13.76
found	C, 61.87; H, 4.71; N,13.58

EXAMPLE 2



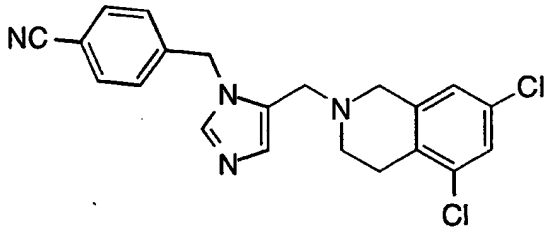
2-(1-(4-Cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

Following the procedure described for Example 1, Step 6 but using 1,2,3,4-tetrahydroisoquinoline, the title compound was obtained as a white solid.

Analysis for $C_{21}H_{20}N_4$

Calcd.	C, 76.80; H, 6.14; N,17.06
found	C, 76.50; H, 5.93; N,16.94

EXAMPLE 3



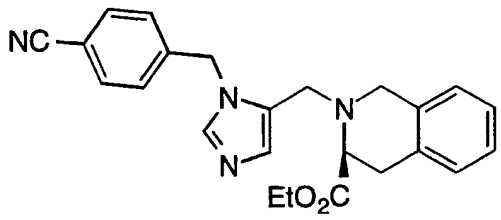
5,7-Dichloro-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

Following the procedure described for Example 1, Step 6 but using 5,7-dichloro-1,2,3,4-tetrahydroisoquinoline, the title compound was obtained as a white solid.

Analysis for $C_{21}H_{18}N_4Cl_2$

Calcd.	C, 63.48; H, 4.57; N,14.10
found	C, 63.53; H, 4.67; N,14.30

EXAMPLE 4



3(S)-Carboethoxy-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride salt

Step 1: 3(S)-Carboethoxy-1,2,3,4-tetrahydroisoquinoline

The title compound was obtained from N-Boc-L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Bachem) using standard amino acid chemical procedures.

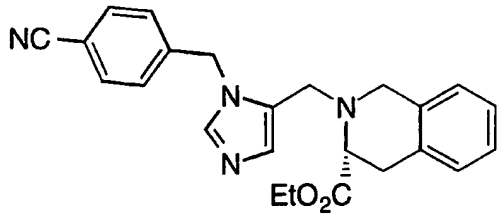
Step 2: 3(S)-Carboethoxy-2-(1-(4-cyanobenzyl)imidazol-5-ylmethyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride salt

Following the procedure described for Example 1, Step 6 but using 3(S)-carboethoxy-1,2,3,4-tetrahydroisoquinoline, the title compound was obtained (after treatment with HCl in ether) as a white solid.

Analysis for $C_{24}H_{24}N_4O_2 \cdot 2HCl$

Calcd.	C, 58.98; H, 5.71; N,11.46
found	C, 58.99; H, 5.63; N,11.39

EXAMPLE 5



3(R)-Carboethoxy-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline Dihydrochloride salt

Step 1: 3(R)-Carboethoxy-1,2,3,4-tetrahydroisoquinoline

The title compound was obtained from N-Boc-D-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Bachem) using standard amino acid chemical procedures.

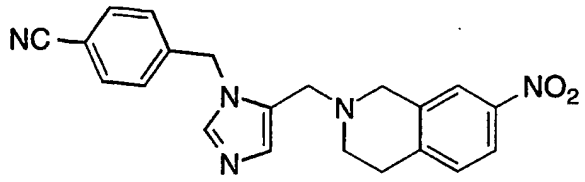
Step 2: 3(R)-Carboethoxy-2-(1-(4-cyanobenzyl)imidazol-5-ylmethyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride salt

Following the procedure described for Example 1, Step 6 but using 3(R)-carboethoxy-1,2,3,4-tetrahydroisoquinoline, the title compound was obtained (after treatment with HCl in ether) as a white solid.

Analysis for $C_{24}H_{24}N_4O_2 \cdot 2HCl$

Calcd.	C, 55.77; H, 5.77; N,10.84
found	C, 55.69; H, 5.77; N,10.92

EXAMPLE 6

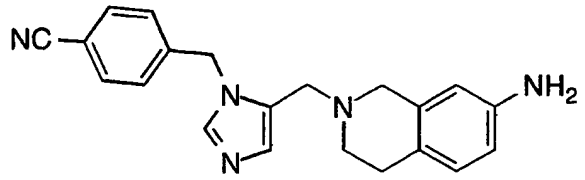


7-Nitro-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

Following the procedure described for Example 1, Step 6 but using 7-nitro-1,2,3,4-tetrahydroisoquinoline, the title compound was obtained (after treatment with HCl in ether) as a white solid.
Analysis for $C_{21}H_{19}N_5O_2 \cdot 1HCl \cdot 2H_2O \cdot 0.1EtOAc$

Calcd.	C, 56.52; H, 5.50; N,15.40
found	C, 56.57; H, 5.05; N,15.15

EXAMPLE 7



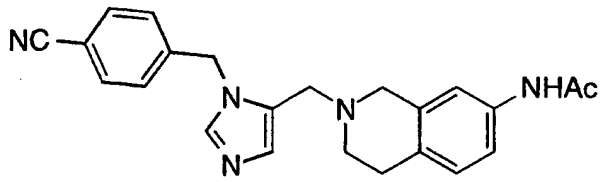
7-Amino-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline tris Trifluoroacetate

A solution of 7-nitro-1,2,3,4-tetrahydroisoquinoline (Example 6, 252 mg) in EtOAc (20 mL) was purged with argon and 10% palladium on carbon (100 mg) added. The mixture was then stirred under an atmosphere of hydrogen gas for 16 h. After filtration and removal of the solvent, the title compound was obtained as a white solid following purification by reverse phase HPLC
Analysis for $C_{21}H_{21}N_5 \cdot 3.2TFA \cdot 1H_2O$

Calcd.	C, 45.31; H, 3.64; N,9.64

found C, 45.35; H, 3.52; N,9.84

EXAMPLE 8

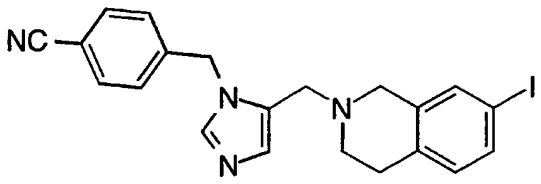


7-Acetamido-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline bis hydrochloride salt

A solution of 7-amino-1,2,3,4-tetrahydroisoquinoline tris trifluoroacetate (Example 7, 119 mg, 0.16 mmol) and triethylamine (80 µL, 0.57 mmol) in THF (2 mL) was treated with acetylchloride (12 µL, 0.16 mmol) and stirred for 16 h. The mixture was poured into saturated aqueous $NaHCO_3$, extracted with EtOAc, washed with water then brine, dried ($MgSO_4$) and concentrated. The residue was purified by reverse phase HPLC (gradient elution with water/acetonitrile containing 0.1% TFA) and the product converted to the HCl salt. Analysis for $C_{23}H_{23}N_5O \cdot 2HCl \cdot 2H_2O \cdot 0.3EtOAc$

Calcd. C, 55.80; H, 6.08; N,13.45
found C, 55.99; H, 6.11; N,13.44

EXAMPLE 9



7-Iodo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline bis hydrochloride salt

Step 1: Preparation of 7-amino-2-trifluoroacetoxy-1,2,3,4-tetrahydroisoquinoline

A solution of 7-nitro-2-trifluoroacetoxy-1,2,3,4-tetrahydroisoquinoline (Stokker, *Tetrahedron Letts.*, **1996**, *37*, 5453; 3.64 g, 13.3 mmol) in 100 mL EtOH at room temperature was was purged with argon and 10% palladium on carbon (300 mg) added. The mixture was then stirred under an atmosphere of hydrogen gas for 2 h. then filtered and the solvent removed in vacuo to yield a white solid which was sufficiently pure for use in the next step.

Step 2: Preparation of 7-iodo-2-trifluoroacetoxy-1,2,3,4-tetrahydroisoquinoline

The aniline prepared above (3.34 g, 13.7 mmol) was suspended in 30 mL 3N HCl, cooled to 0°C and treated with a solution of $NaNO_2$ (1.04 g, 15.1 mmol) in 7 mL H_2O. After 30 minutes, a solution of KI (6.8 g, 41.1 mmol) in 10 mL H_2O was added to the reaction mixture and stirring was continued for 45 minutes. The mixture was partitioned between $CHCl_3$ and water, the organic layer was washed with aqueous $NaHSO_3$ then brine, dried and evaporated. Chromatography of the residue (hexane/EtOAc 5:1) afforded the title compound as a colorless oil.

Step 3: Preparation of 7-iodo-1,2,3,4-tetrahydroisoquinoline

The iodide from Step 2 (2.8 g, 7.9 mmol) in THF (15 mL) and MeOH (30 mL) was treated with 1N LiOH (24 mL, 24 mmol) for 1

h at room temperature. After pouring into brine, the solution was extracted 2X EtOAc, washed with water then brine, dried and evaporated to give the title compound as a solid.

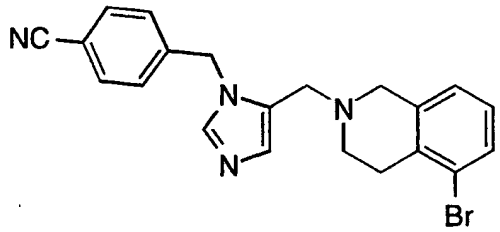
Step 4: 7-iodo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline bis hydrochloride salt

Following the procedure described for Example 1, Step 6 but using 7-iodo-1,2,3,4-tetrahydroisoquinoline the title compound was obtained as the HCl salt as a white solid.

Analysis for $C_{21}H_{19}N_4I \cdot 2HCl \cdot 0.1EtOAc$

Calcd.	C, 45.43; H, 4.47; N,9.90
found	C, 45.40; H, 4.33; N,9.92

EXAMPLE 10



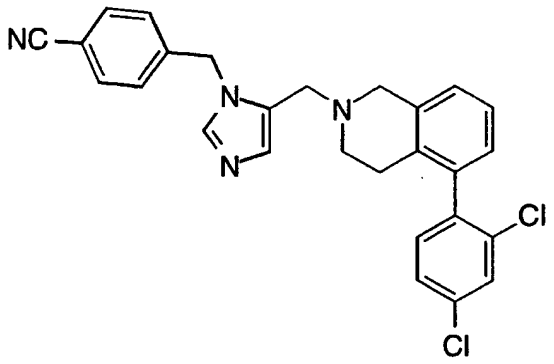
5-Bromo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

Following the procedure described for Example 1, Step 6 but using 5-bromo-1,2,3,4-tetrahydroisoquinoline the title compound was obtained as a white solid.

Analysis for $C_{21}H_{19}N_4Br$

Calcd.	C, 57.09; H, 4.34; N,12.48
found	C, 57.32; H, 4.43; N,12.41

EXAMPLE 11

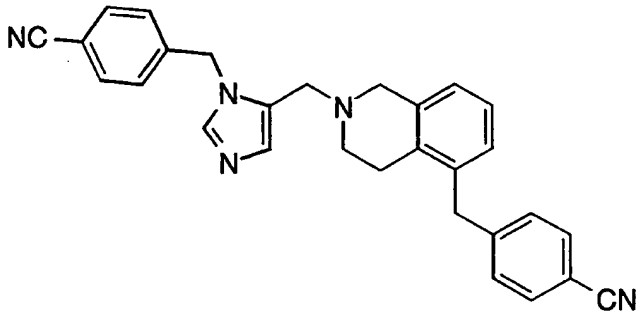


5-(2,4-Dichlorophenyl)-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

A solution of 5-bromo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline (Example 10; 100 mg, 250 0.25 mmol), 2,4-dichlorophenyl boronic acid (53 mg, 0.275 mmol) and tetrakis(triphenylphosphine)palladium(0) in DME (2 mL) and water (0.5 mL) was heated to 80°C for 20 h. The mixture was partitioned between water and EtOAc, washed with aqueous $NaHCO_3$, water (2X), dried and evaporated. Column chromatography of the residue (silica gel; $CHCl_3$/MeOH 80:1) afforded the title compound as a white solid.

FAB ms (m+1) 473.2

EXAMPLE 12



5-(4-Cyanobenzyl) -2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

Step 1: Preparation of 5-(4-cyanobenzyl)-2-trifluoroacetoxy-1,2,3,4-tetrahydroisoquinoline

Dibromoethane (1 drop) was added to zinc dust (195 mg, 3.0 mmol) followed by THF (5 mL) and the slurry was stirred under argon for 15 minutes. 4-Cyanobenzylbromide (510 mg, 2.6 mmol) was added dropwise over 15 minutes and the mixture then stirred for 2 h. Bis(triphenylphosphine) nickel chloride (130 mg, 0.2 mmol) and 5-bromo-2-trifluoroacetoxy-1,2,3,4-tetrahydroisoquinoline (616 mg, 2 mmol) were added in one portion at room temperature. After 30 minutes, the reaction was heated to 40°C for 3 h.then cooled and quenched with saturated NH_4Cl solution. The mixture was poured into water, extracted with EtOAc, washed with water, dried and the solvent removed in vacuo. Column chromatography of the dark mixture (silica gel; hexane/EtOAc 20:1 then 10:1 then 4:1) afforded the title compound.
FAB ms (m+1) 345.15

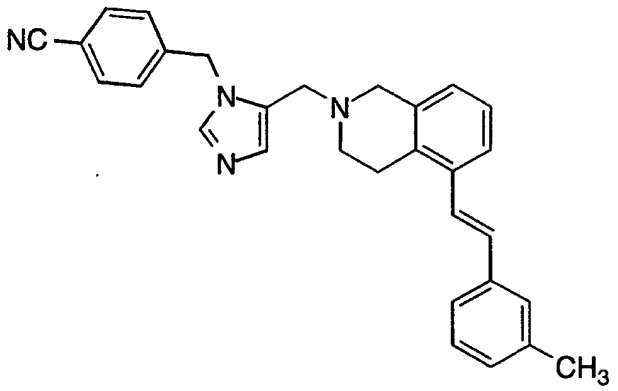
Step 2: Preparation of 5-(4-cyanobenzyl) -1,2,3,4-tetrahydroisoquinoline

The trifluoroacetate from Step 1 was hydrolysed following the procedure described for Example 9, Step 3 to give the title compound.

Step 3 5-(4-cyanobenzyl) -2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

Following the procedure described for Example 1, Step 6 but using 5-(4-cyanobenzyl)-1,2,3,4-tetrahydroisoquinoline the title compound was obtained as a white solid. FAB ms (m+1) 444.25; m.p. 195-196°C

EXAMPLE 13



5-(2-(3-Tolyl)vinyl)-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline Bis trifluoroacetate salt

Step 1: Preparation of 5-(2-(3-tolyl)vinyl)-2-trifluoroacetoxy-1,2,3,4-tetrahydroisoquinoline

A solution of 5-bromo-2-trifluoroacetoxy-1,2,3,4-tetrahydroisoquinoline (616 mg, 2 mmol), 3-vinyltoluene (330 mg, 2.5 mmol), tri-o-tolylphosphine (50 mg) and palladium acetate (20 mg) in triethylamine (1 mL) were heated in a pressure bomb at 100°C for 8 h. Column chromatography of the dark mixture (silica gel; hexane/EtOAc 40:1 then 20:1) afforded the title compound.
FAB ms (m+1) 346.18

Step 2: Preparation of 5-(3-tolyl)vinyl)-1,2,3,4-tetrahydroisoquinoline

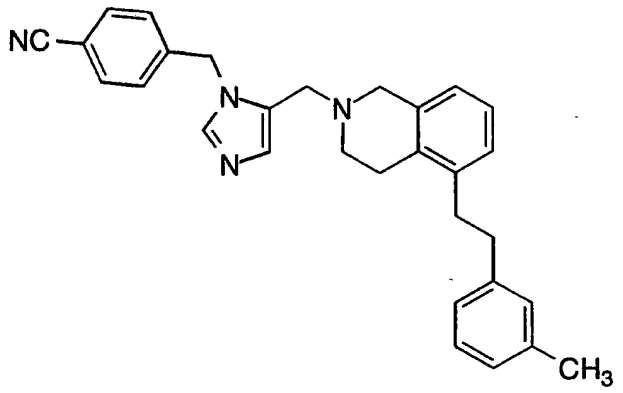
The trifluoroacetate from Step 1 was hydrolysed following the procedure described for Example 9, Step 3 to give the title compound.

Step 3 5-(3-tolyl)vinyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl) -1,2,3,4-tetrahydroisoquinoline

Following the procedure described for Example 1, Step 6 but using 5-(3-tolyl)vinyl)-1,2,3,4-tetrahydroisoquinoline the title compound was obtained as a TFA salt following HPLC purification.
FAB ms (m+1) 445.04.
Analysis for $C_{30}H_{28}N_4 \cdot 2TFA$

Calcd.	C, 56.49; H, 4.41; N,7.55
found	C, 56.45; H, 4.39; N,7.16

EXAMPLE 14



5-(2-(3-Tolyl)ethyl)-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline bis trifluoroacetate salt

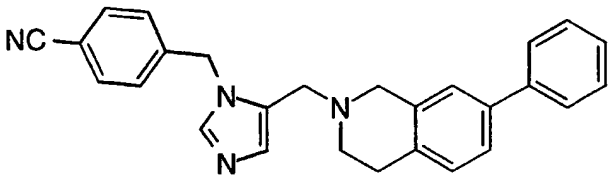
Step 1: Preparation of 5-(3-tolyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

The stilbene from Example 13, Step 2 (242 mg, 1 mmol) was hydrogenated in 10 mL EtOH with 50 mg 10% palladium on carbon and hydrogen gas (balloon). Filtration through celite and removal of the solvent gave the title compound.

Step 2 5-(3-Tolyl)ethyl)-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

Following the procedure described for Example 1, Step 6 but using 5-(3-tolyl)ethyl)-1,2,3,4-tetrahydroisoquinoline the title compound was obtained as a TFA salt following HPLC purification. FAB ms (m+1) 447.21.

EXAMPLE 15



7-Phenyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

Step 1: Preparation of 7-bromo-N-Boc-1,2,3,4-tetrahydroisoquinoline

7-Bromo-1,2,3,4-tetrahydroisoquinoline (1.58 g, 7.45 mmol) in DMF (30 mL) was treated with triethylamine (1.04 mL, 7.45 mmol) and $(Boc)_2O$ (1.75 g, 8 mmol) for 16 h. The DMF was removed in vacuo and the residue partitioned between water and EtOAc. Extracted with EtOAc (3X), washed with saturated $NaHCO_3$ then brine, dried and evaporated. Chromatography of the residue (silica gel; hexane/EtOAc 9:1) afforded the title compound as an oil.

Step 2: Preparation of 7-phenyl-N-Boc-1,2,3,4-tetrahydroisoquinoline

7-Bromo-2-(trifluoroacetoxy)-1,2,3,4-tetrahydroisoquinoline was coupled with phenyl boronic acid following the procedure of Example 11 to give the title compound as a viscous oil.

Step 3: Preparation of 7-phenyl-1,2,3,4-tetrahydroisoquinoline

HCl gas was bubbled through a solution of the Boc-amine from Step 2 (0.72 g) in EtOAc (25 mL) at -25°C for 10 minutes. The solution was stoppered and stirred at 0°C for 1.5 h. then the solvent was removed in vacuo. Trituration of the solid with EtOAc (25 mL) and filtration afforded the title compound as a solid

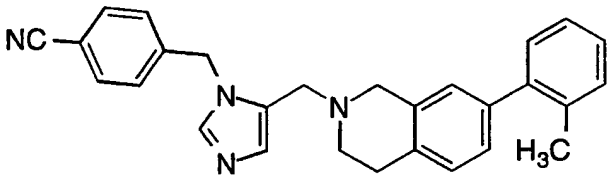
Step 4: Preparation of 7-phenyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

Following the procedure described for Example 1, Step 6 but using 7-phenyl-1,2,3,4-tetrahydroisoquinoline the title compound was obtained as a white solid.

Analysis for $C_{27}H_{24}N_4$

Calcd.	C, 80.17; H, 5.98; N,13.85
found	C, 80.36; H, 5.98; N,14.12

EXAMPLE 16



7-(2-Tolyl)-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

Step 1: Preparation of 7-bromo-N-Boc-1,2,3,4-tetrahydroisoquinoline

7-Bromo-1,2,3,4-tetrahydroisoquinoline (1.58 g, 7.45 mmol) in DMF (30 mL) was treated with triethylamine (1.04 mL, 7.45 mmol) and (Boc)2O (1.75 g, 8 mmol) for 16 h. The DMF was removed in vacuo and the residue partitioned between water and EtOAc. Extracted with EtOAc (3X), washed with saturated NaHCO3

then brine, dried and evaporated. Chromatography of the residue (silica gel; hexane/EtOAc 9:1) afforded the title compound as an oil

Step 2: Preparation of 7-(2-tolyl)-N-Boc-1,2,3,4-tetrahydroisoquinoline

7-Bromo-2-(trifluoroacetoxy)-1,2,3,4-tetrahydroisoquinoline was coupled with 2-methylphenyl boronic acid following the procedure of Example 11 to give the title compound as a viscous oil.

Step 3: Preparation of 7-(2-tolyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride salt

HCl gas was bubbled through a solution of the Boc-amine from Step 2 (0.72 g) in EtOAc (25 mL) at -25°C for 10 minutes. The solution was stoppered and stirred at 0°C for 1.5 h. then the solvent was removed in vacuo. Trituration of the solid with EtOAc (25 mL) and filtration afforded the title compound as a solid

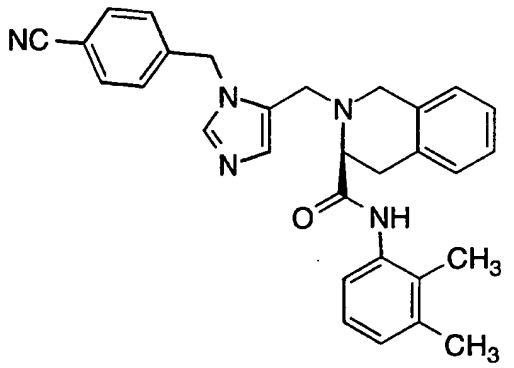
Step 4: Preparation of 7-(2-tolyl)-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

Following the procedure described for Example 1, Step 6 but using 7-(2-tolyl)-1,2,3,4-tetrahydroisoquinoline the title compound was obtained as a white solid.

Analysis for $C_{28}H_{26}N_4 \cdot 2HCl \cdot 1.5H_2O$

Calcd.	C, 64.86; H, 6.03; N,10.81
found	C, 65.04; H, 6.17; N,10.67

EXAMPLE 17



N-(2,3-Dimethylphenyl)-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxamide bis trifluoroacetate salt

Step 1: N-(2,3-dimethylphenyl) 1,2,3,4-tetrahydroisoquinoline-3(S)-carboxamide

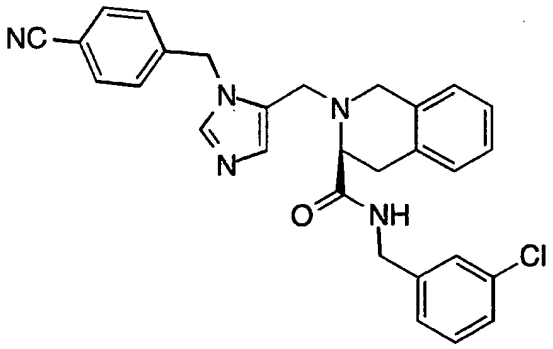
N-Boc-L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Bachem) was coupled with 2,3-dimethyl aniline using standard peptide coupling procedures. The product was deprotected using TFA in CH_2Cl_2 to give the title compound.

Step 2: Preparation of N-(2,3-dimethylphenyl)-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxamide bis trifluoroacetate salt

Following the procedure described for Example 1, Step 6 but using N-(2,3-dimethylphenyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxamide the title compound was obtained as a white solid.
Analysis for $C_{30}H_{29}N_5O \cdot 2.6TFA \cdot 0.2H_2O$

Calcd.	C, 54.51; H, 4.16; N,9.03
found	C, 54.58; H, 4.22; N,8.82

EXAMPLE 18



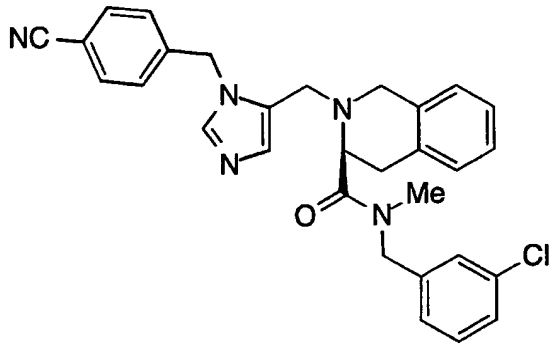
N-(3-Chlorobenzyl) 2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxamide bis trifluoroacetate salt

Following the procedure described for Example 17 but using 3-chlorobenzylamine, the title compound was obtained as a white solid.

Analysis for $C_{29}H_{26}N_5OCl \cdot 2.2TFA$

Calcd.	C, 53.71; H, 3.81; N,9.38
found	C, 53.67; H, 3.76; N,9.25

EXAMPLE 19



N-(3-Chlorobenzyl),N-methyl 2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline-3(s)-carboxamide bis trifluoroacetate salt

Step 1: Preparation of N-(3-chlorobenzyl) 2-Boc-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxamide

N-Boc-L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Bachem) was coupled with 3-chlorobenzylamine using standard peptide coupling procedures to give the title compound.

Step 2: Preparation of N-(3-chlorobenzyl), N-methyl 2-Boc-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxamide

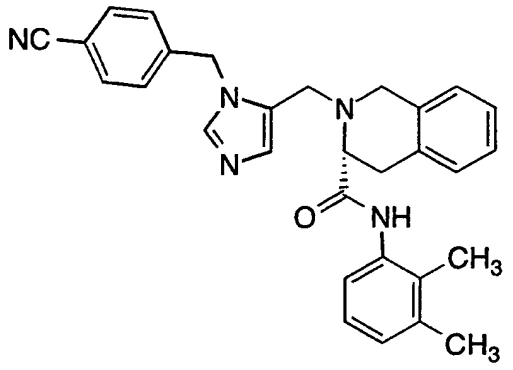
The product from Step 1 (390 mg, 0.945 mmol) was dissolved in dry DMF (5 mL) at 0°C and then treated with NaH (49 mg, 1.23 mmol). After 5 minutes, methyl iodide (76 µL, 1.23 mmol) was added and the reaction was stirred for 16 h. The mixture was poured into water and extracted with EtOAc, washed aqueous $NaHCO_3$ then brine, dried and evaporated to give the title product which was used as such.

Step 3: Preparation of N-(3-chlorobenzyl),N-Methyl 2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxamide bis trifluoroacetate salt

Following the procedure described for Example 17 but using N-methyl 2-Boc-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxamide, the title compound was obtained as a white solid.
Analysis for $C_{30}H_{28}N_5OCl \cdot 2.3TFA$

Calcd.	C, 53.81; H, 3.95; N,9.07
found	C, 53.91; H, 3.87; N,9.04

EXAMPLE 20



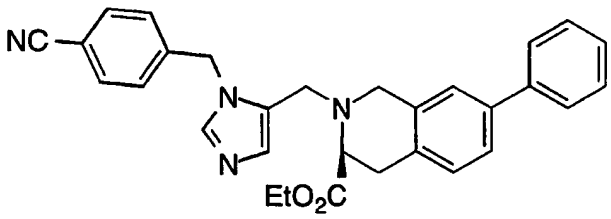
N-(2,3-Dimethylphenyl)-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline-3(R)-carboxamide bis hydrochloride salt

Following the procedure described for Example 17 but using N-Boc-D-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Bachem) the title compound was obtained as a white solid.

Analysis for $C_{30}H_{29}N_5O \cdot 2HCl \cdot H_2O$

Calcd.	C, 63.60; H, 5.87; N,12.36
found	C, 63.50; H, 5.99; N,12.36

EXAMPLE 21



3(S)-Carboethoxy-7-phenyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride salt

Step 1: Preparation of 2-Boc-3(S)-carboethoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline

The title compound was obtained from L-2-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Bachem) using

standard amino acid chemical procedures (EtOH/HCl followed by $(Boc)_2O$/triethylamine in CH_2Cl_2).

Step 2: Preparation of 2-Boc-3(S)-carboethoxy-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

The phenol from Step 1 (0.6 g, 1.87 mmol) was dissolved in CH_2Cl_2 (20 mL) and triethylamine (0.78 mL, 5.6 mmol) at room temperature. Trifluoromethanesulfonic anhydride (0.345 mL, 2.06 mmol) was added and the mixture stirred for 16 h. The solution was poured into aqueous NaHCO3 and extracted with CH_2Cl_2 (3X), washed with brine, dried and concentrated to give a brown oil. Column chromatography (silica gel; hexane/EtOAc 4:1) provided the title compound as an oil.

Step 3: Preparation of 2-Boc-3(S)-carboethoxy-7-phenyl-1,2,3,4-tetrahydroisoquinoline

The triflate from Step 2 was coupled with phenyl boronic acid following the procedure of Example 11 to give the title compound as an oil.

Step 4: Preparation of 3(S)-carboethoxy-7-phenyl-1,2,3,4-tetrahydroisoquinoline hydrochloride

The Boc-amine from Step 3 (48 mg) was deprotected using 75 mL EtOAc saturated with HCl. Removal of the solvent in vacuo gave the title compound as a white solid.

Step 5: Preparation of 3(S)-carboethoxy-7-phenyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride salt

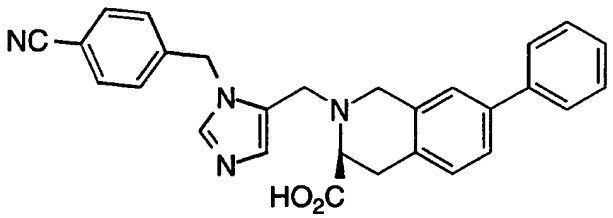
Following the procedure described for Example 1, Step 6 but using the product from Step 4 the title compound was obtained as a white solid.

Analysis for $C_{30}H_{28}N_4O_2 \cdot 2HCl \cdot 0.2H_2O$

Calcd. C, 65.14; H, 5.54; N,10.13

found C, 65.12; H, 5.58; N,9.77

EXAMPLE 22



3(S)-Carboxylic acid-7-phenyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

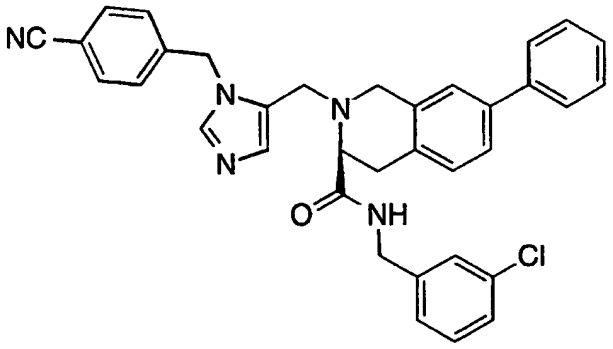
3(S)-Carboethoxy-7-phenyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline (100 mg, 0.21 mmol) from Example 21 was hydrolysed in THF (5 mL) and water (5 mL) using 1N LiOH (0.84 mL, 0.84 mmol). After 16 h, the mixture was neutralized with HCl (pH~7) and extracted with EtOAc (3X), washed with brine, dried and evaporated to give the title compound as a white solid.

Analysis for $C_{28}H_{24}N_4O_2 \cdot 1.1EtOAc$

Calcd. C, 71.34; H, 6.06; N,10.27

found C, 71.25; H, 5.77; N,10.55

EXAMPLE 23



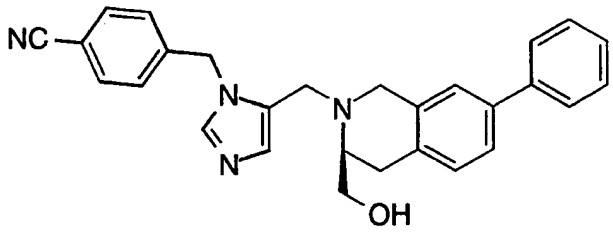
N-(3-Chlorobenzyl)-7-phenyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxamide bis hydrochloride salt

Following the procedure described for Example 18 but using 3(S)-carboxylic acid-7-phenyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline from Example 22, the title compound was obtained as a white solid.

Analysis for $C_{35}H_{30}N_5OCl \cdot 2.35HCl \cdot 0.15EtOAc$

	Calcd.	C, 63.72; H, 5.04; N,10.44
	found	C, 63.69; H, 5.43; N,10.54

EXAMPLE 24



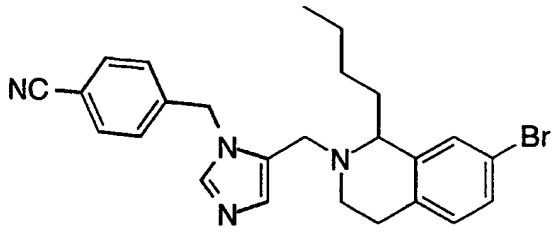
3(S)-Hydroxymethyl-7-phenyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline bis hydrochloride salt

3(S)-Carboethoxy-7-phenyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline (150 mg, 0.32 mmol) from Example 21 was dissolved in THF (3 mL) and treated with $LiBH_4$ (13.7 g, 0.64 mmol). The solution was heated at 50°C for 3 h then quenched with 1N HCl and extracted with EtOAc (3X), washed with brine, dried and evaporated. The residue was purified by preparative HPLC (gradient elution with water/acetonitrile containing 0.1% TFA), the product neutralized and converted to the HCl salt using 1N HCl in ether to give the title compound as a white solid.

Analysis for $C_{28}H_{26}N_4O_2 \cdot 2.5HCl \cdot 0.5EtOAc$

	Calcd.	C, 63.24; H, 5.75; N,9.83
	found	C, 63.22; H, 5.88; N,10.00

EXAMPLE 25



1(R,S)-n-Butyl-7-bromo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline Dihydrochloride salt

Step 1: Preparation of N-pentanoyl 2-(4-bromophenethyl)amine

A solution of 4-bromophenethylamine (3.2 g, 16 mmol) and triethylamine (2.34 mL, 16.8 mmol) in CH_2Cl_2 at 0°C was treated with valeryl chloride (2.03 g, 16.8 mmol) and then stirred at room temperature for 16 h. The solvent was removed in vacuo, EtOAc then added and the solution washed with brine, 10% $KHSO_4$ solution, saturated $NaHCO_3$ and then brine. After drying, the solvent was removed to give the title compound as a solid.

Step 2: Preparation of 1-n-butyl-7-bromo-3,4-dihydroisoquinoline

Following the procedure described by Larsen et al (*J. Org. Chem.*, 1991, *56*, 6034) the amide from Step 1 (0.853 g, 3 mmol) was dissolved in CH_2Cl_2 (25 mL) at 0°C and was treated with oxalyl chloride (0.288 mL, 3.3 mmol). The mixture was stirred at room temperature for 18 h then $FeCl_3$ (anhydrous; 0.584 g, 3.6 mmol) was added at 0°C and the mixture was then stirred for a further 18 h at room temperature. The reaction was quenched with 2N HCl, stirred for 1 h then extracted with CH_2Cl_2, washed with brine, dried and the solvent removed to give a solid. This solid was stirred in MeOH (19 mL) and conc. H_2SO_4 (1 mL) at reflux for 18 h, the mixture was cooled and the methanol removed *in vacuo*. Water and EtOAc was added to the residue, and the organic layer was washed twice with 1N HCl. The combined aqueous extracts were basified with conc. NH_4OH,

extracted with CH_2Cl_2, washed with brine, dried and the solvent removed to give the title compound as a viscous oil.

Step 3: Preparation of 1(R,S)-n-butyl-7-bromo-1,2,3,4-tetrahydroisoquinoline

The imine from Step 2 was dissolved in absolute EtOH (25 mL) and $NaBH_4$ (0.303 g, 8.0 mmol) was added. After 2 h, the solvent was removed and the residue treated with 1N HCL. Conc. NH_4OH was added to the solution which was then extracted with CH_2Cl_2 (3X), washed with brine, dried and concentrated to give the title compound as a viscous oil which was used as such.

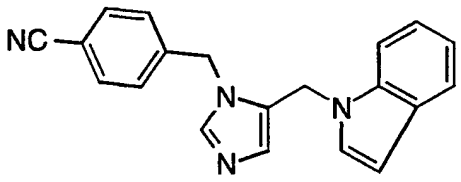
Step 4: Preparation of 1(R,S)-n-butyl-7-bromo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride salt

Following the procedure described for Example 1, Step 6 but using the product from Step 3 the title compound was obtained as a white solid.

Analysis for $C_{25}H_{27}N_4Br \cdot 2.5HCl \cdot 1.5H_2O$

Calcd.	C, 51.62; H, 5.63; N,9.63
found	C, 51.66; H, 5.48; N,9.61

EXAMPLE 26



1-(1-(4-Cyanobenzyl)-5-imidazolylmethyl)indole

Step 1: Preparation of 1-(4-cyanobenzyl)-5-(chloromethyl)imidazole hydrochloride

A suspension of 1-(4-cyanobenzyl)-5-(hydroxymethyl)-imidazole from Example 1, Step 4 (3.1 g) in thionyl chloride (20 mL)

was heated at 60°C for 16 h. The reaction was concentrated *in vacuo*, azeotroped with $CHCl_3$ and filtered to give the title compound as a pale yellow solid which was sufficiently pure for use in the next step without further purification.

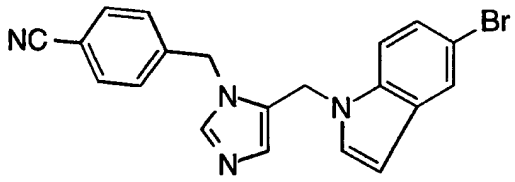
Step 2: Preparation of 1-(1-(4-cyanobenzyl)-5-imidazolylmethyl) indole

Indole (117 mg, 1.0 mmol) dissolved in DMF (15 mL) was treated with NaH (48 mg, 2 mmol) and stirred for 30 minutes before the addition of the chloride from Step 1 (268 mg, 1 mmol). The mixture was stirred for 16 h, poured into water, extracted with EtOAc (3X), washed with aqueous $NaHCO_3$ then brine, dried and evaporated to give an oil. Chromatography of this oil (silica gel; 2.5%MeOH in $CHCl_3$) gave an oil which solidified when stirred in ether. Filtration afforded the title product as an off-white solid.

Analysis for $C_{20}H_{16}N_4$

Calcd.	C, 76.90; H, 5.16; N,17.94
found	C, 76.66; H, 5.20; N,17.72

EXAMPLE 27



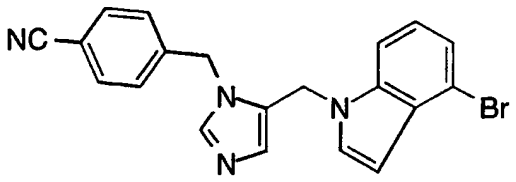
5-Bromo-1-(1-(4-cyanobenzyl)-5-imidazolylmethyl)indole

Following the procedure described for Example 26, Step 2 but using 5-bromoindole (Aldrich) the title compound was obtained as a solid.

Analysis for $C_{20}H_{15}N_4Br$

Calcd.	C, 61.39; H, 3.86; N,14.32
found	C, 61.38; H, 3.98; N,14.35

EXAMPLE 28



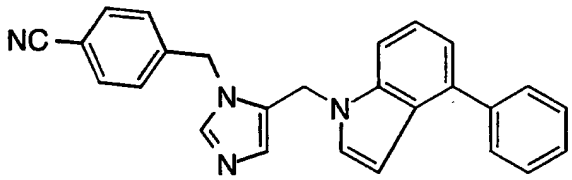
4-Bromo-1-(1-(4-cyanobenzyl)-5-imidazolylmethyl)indole

Following the procedure described for Example 26, Step 2 but using 4-bromoindole (TCI) the title compound was obtained as a solid.

Analysis for $C_{20}H_{15}N_4Br$

Calcd.	C, 61.39; H, 3.86; N,14.32
found	C, 61.40; H, 3.89; N,14.34

EXAMPLE 29



4-Phenyl-1-(1-(4-cyanobenzyl)-5-imidazolylmethyl)indole

Step 1: Preparation of 4-phenylindole

Following the procedure described for Example 21, Steps 2 and 3, 5-hydroxyindole (Aldrich) was converted into the title compound.

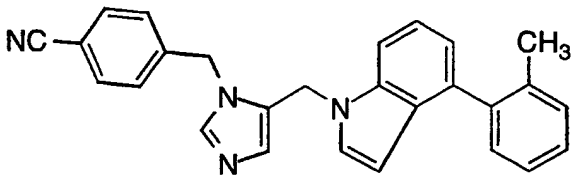
Step 2: Preparation of 4-phenyl-1-(1-(4-cyanobenzyl)-5-imidazolylmethyl)indole

Following the procedure described for Example 26, Step 2 but using 4-phenylindole from Step 1, the title compound was obtained (after HPLC purification) as a TFA salt.

Analysis for $C_{26}H_{20}N_4 \cdot 1.2TFA \cdot 0.75H_2O$

Calcd. C, 63.30; H, 4.25; N,10.40
found C, 63.29; H, 4.14; N,10.70

EXAMPLE 30



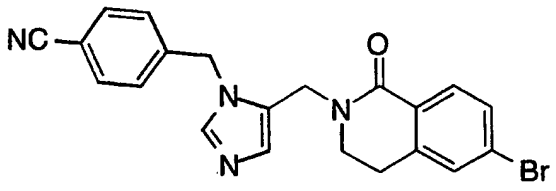
4-(2-Methylphenyl)-1-(1-(4-cyanobenzyl)-5-imidazolylmethyl)indole

Following the procedure described for Example 21, Step 3, 4-bromo-1-(1-(4-cyanobenzyl)-5-imidazolylmethyl)indole (Example 28) was coupled with 2-methylphenyl boronic acid to give the title compound.

Analysis for $C_{27}H_{22}N_4 \cdot 0.25CHCl_3$

Calcd. C, 75.70; H, 5.19; N,12.96
found C, 76.06; H, 5.35; N,13.07

EXAMPLE 31



6-Bromo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-3,4-dihydro-1(1H)-isoquinolinone hydrochloride salt

Step 1: Preparation of 6-Bromo-3,4-dihydro-1(1H)-isoquinolinone

To a rapidly stirred solution of 5-bromo-1-indanone (Aldrich) (15.0 g, 71.1 mmol) in benzene (200 mL) and H_2SO_4 (38 mL) was added NaN_3 portionwise over 20 minutes. The mixture was

diluted EtOAc, washed with water then brine, dried and evaporated. Chromatography of the residue (silica gel; hexane/EtOAc 1:1) afforded the title compound as a solid.

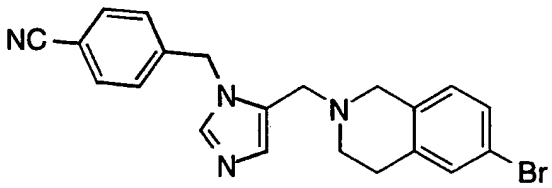
Step 2: Preparation of 6-bromo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-3,4-dihydro-1(1H)-isoquinolinone hydrochloride salt

Following the procedure described for Example 26, Step 2, but using 6-bromo-3,4-dihydro-1(1H)-isoquinolinone from Step 1, the title compound was obtained.

Analysis for $C_{21}H_{17}N_4Br \cdot 1.5HCl \cdot 1.5H_2O$

Calcd.	C, 50.14; H, 4.31; N,11.14
found	C, 50.55; H, 4.03; N,10.74

EXAMPLE 32



6-Bromo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

Step 1: Preparation of 6-bromo-1,2,3,4-tetrahydroisoquinoline

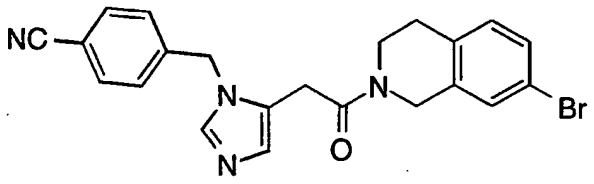
A solution of 6-bromo-3,4-dihydro-1(1H)-isoquinolinone (Example 31, Step 1; 5.5 g, 1.0 mmol) in THF (25 mL) was treated with 1M BH_3 in THF (5 mL, 5 mmol) and heated at reflux for 20 h. To the mixture was added MeOH (5 mL), the solvent removed and the residue heated with 2N HCl for 3 h. The reaction was cooled, made basic with aqueous NH_4OH and extracted with CH_2Cl_2, dried and evaporated to give the title compound as a gum which was used as such.

Step 2: Preparation of 6-Bromo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

Following the procedure described for Example 1, Step 6 but using 6-bromo-1,2,3,4-tetrahydroisoquinoline from Step 1 the title compound was obtained.
Analysis for $C_{21}H_{19}N_4Br$

Calcd.	C, 61.92; H, 4.70; N,13.76
found	C, 61.59; H, 4.65; N,13.49

EXAMPLE 33



7-Bromo-2-(1-(4-cyanobenzyl)-5-imidazolylacetyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride

Step 1: Preparation of 1H-imidazole-4- acetic acid methyl ester hydrochloride

A solution of 1H-imidazole-4-acetic acid hydrochloride (4.00g, 24.6 mmol) in methanol (100 mL) was saturated with gaseous hydrogen chloride. The resulting solution was allowed to stand at room temperature for 18h. The solvent was evaporated in vacuo to afford the title compound as a white solid.
^1H NMR($CDCl_3$, 400 MHz) δ 8.85(1H, s),7.45(1H, s), 3.89(2H, s) and 3.75(3H, s) ppm.

Step 2: Preparation of 1-(triphenylmethyl)-1H-imidazol-4-ylacetic acid methyl ester

To a solution of 1H-imidazole-4- acetic acid methyl ester hydrochloride (24.85 g, 0.141 mol) in DMF (115 mL) was added triethylamine (57.2 mL, 0.412 mol) and triphenylmethyl bromide (55.3 g, 0.171 mol) and the suspension was stirred for 24 h. After this time, the reaction mixture was diluted with EtOAc (1 L) and water (350 mL).

The organic phase was washed with sat. aqueous $NaHCO_3$ (350 mL), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (SiO_2, 0-100% ethyl acetate in hexanes; gradient elution) to provide the title compound as a white solid.
^1H NMR ($CDCl_3$, 400 MHz) δ 7.35(1H, s), 7.31(9H, m), 7.22(6H, m), 6.76(1H, s), 3.68(3H, s) and 3.60(2H, s) ppm.

Step 3: Preparation of [1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetic acid methyl ester

To a solution of 1-(triphenylmethyl)-1H-imidazol-4-ylacetic acid methyl ester (8.00 g, 20.9 mmol) in acetonitrile (70 mL) was added bromo-p-toluonitrile (4.10g, 20.92 mmol) and heated at 55°C for 3 hr. After this time, the reaction was cooled to room temperature and the resulting imidazolium salt (white precipitate) was collected by filtration. The filtrate was heated at 55°C for 18 h. The reaction mixture was cooled to room temperature and evaporated in vacuo. To the residue was added EtOAc (70 mL) and the resulting white precipitate collected by filtration. The precipitated imidazolium salts were combined, suspended in methanol (100 mL) and heated to reflux for 30 minutes. After this time, the solvent was removed in vacuo, the resulting residue was suspended in EtOAc (75 mL) and the solid isolated by filtration and washed (EtOAc). The solid was treated with sat aq $NaHCO_3$ (300 mL) and CH_2Cl_2 (300 mL) and stirred at room temperature for 2 h. The organic layer was separated, dried ($MgSO_4$) and evaporated in vacuo to afford the title compound as a white solid :
$^1HNMR(CDCl_3$, 400 MHz) δ 7.65(1H, d, J=8Hz), 7.53(1H, s), 7.15(1H, d, J=8Hz), 7.04(1H, s), 5.24(2H, s), 3.62(3H, s) and 3.45(2H, s) ppm.

Step 4: Preparation of [1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetic acid

A solution of [1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetic acid methyl ester (4.44 g, 17.4 mmol) in THF (100 mL) and 1 M lithium hydroxide (17.4 mL, 17.4 mmol) was stirred at room temperature for 18 h. 1 M HCl (17.4 mL) was added and the THF was

removed by evaporation in vacuo. The aqueous solution was lyophilized to afford the title compound containing lithium chloride as a white solid.

^{1}H NMR(CD_3OD, 400 MHz) δ 8.22(1H, s), 7.74(1H, d, J=8.4Hz), 7.36(1H, d, J=8.4Hz), 7.15(1H, s), 5.43(2H, s) and 3.49(2H, s) ppm.

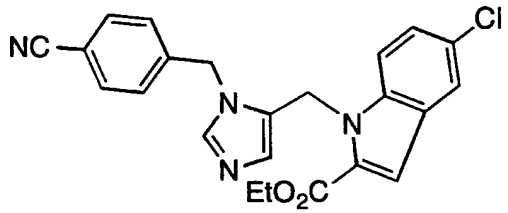
Step 5: Preparation 7-bromo-2-(1-(4-cyanobenzyl)-5-imidazolylacetyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride

The acid from Step 4 (0.575 g, 2 mmol), 7-bromo-1,2,3,4-tetrahydroisoquinoline (0.424 g, 2 mmol) and HOBT (0.297 g, 2.2 mmol) were dissolved in DMF (15 mL) and NMM (0.44 mL, 4 mmol) and EDC (0.46 g, 2.4 mmol) were added. The resulting solution was stirred for 16 h then poured into water and extracted with EtOAc (3X). The EtOAc layers were washed with aqueous NaHCO3 then brine, dried and evaporated to give an oil which was triturated with ether to afford a solid. Purification by preparative HPLC (gradient elution; acetonitrile/ water containing 0.1% HCl) afforded the title compound.

Analysis for $C_{22}H_{19}N_4OBr \cdot 1HCl$

Calcd.	C, 56.00; H, 4.27; N,11.88
found	C, 55.76; H, 4.18; N,11.69

EXAMPLE 34



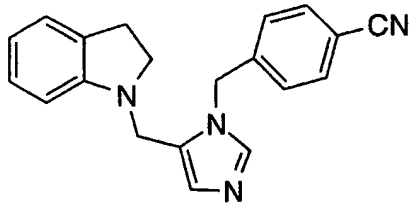
5-Chloro-2-carboethoxy-1-(1-(4-cyanobenzyl)-5-imidazolylmethyl)indole

Following the procedure described for Example 26, Step 2 but using 5-chloro-2-carboethoxyindole (Aldrich) the title compound was obtained as a solid.

Analysis for $C_{23}H_{19}N_4ClO_2$

Calcd. C, 65.95; H, 4.57; N,13.38
found C, 66.03; H, 4.62; N,12.92

EXAMPLE 35



1-(4-Cyanobenzyl)-5-(1-indolinylmethyl)imidazole hydrochloride

To a solution of indoline (126 mg, 1.06 mmol) in 3 mL of dry DMF was added sodium hydride (93.0 mg, 2.33 mmol, 60% dispersion in mineral oil) at room temperature. After one hour, the solution was cooled to -50 °C and the chloride described in Example 26, Step 1 (284 mg, 1.06 mmol) was added as a solid. The reaction was slowly warmed to room temperature over 16 hours, poured onto water, and extracted with methylene chloride (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide a yellow oil. The crude product was purified by column chromatography (1-5% MeOH/$CHCl_3$) and then treated with HCl to provide the title compound as a white solid.
MS (FAB) m+1 = 315. Elemental analysis for $C_{20}H_{18}N_4 \cdot 2.50\ HCl \cdot .25\ H_2O$ calc. C, 58.58; H, 5.16; N, 13.66; found C, 58.61; H, 4.82; N, 13.80.

Using the methods described above, the following compounds were prepared:

1-(4-cyanobenzyl)-5-(1-indazolylmethyl)imidazole hydrochloride
Analysis calculated for formula: $C_{19}H_{15}N_5 \bullet 1.70\ HCl \bullet H_2O$
C, 51.18; H, 5.52; N, 12.24;
Found C, 51.09; H, 5.25; N, 12.26.

1-(4-cyanobenzyl)-5-(1-tetrahydroquinolinylmethyl)imidazole hydrochloride

Analysis calculated for formula: $C_{21}H_{20}N_4 \bullet 2.25$ HCl

C, 61.44; H, 5.46; N, 13.65;

Found C, 61.45; H, 5.62; N, 13.54.

5-(1-benzotriazolylmethyl)-1-(4-cyanobenzyl)imidazole hydrochloride

Analysis calculated for formula: $C_{18}H_{14}N_6 \bullet 1.25$ HCl $\bullet$ .15 Et_2O

C, 60.20; H, 4.55; N, 22.65;

Found C, 60.17; H, 4.31; N, 22.69.

5-(1-benzoimidazolylmethyl)-1-(4-cyanobenzyl)imidazole hydrochloride

Analysis calculated for formula: $C_{19}H_{15}N_5 \bullet 2.50$ HCl $\bullet$ 1.35 CH_2Cl_2

C, 47.07; H, 3.92; N, 13.49;

Found C, 47.13; H, 4.32; N, 13.47.

5-[1-(7-azaindolyl)methyl]-1-(4-cyanobenzyl)imidazole hydrochloride

Analysis calculated for formula: $C_{19}H_{15}N_5 \bullet 1.85$ HCl $\bullet$ 1.05 CH_2Cl_2

C, 51.23; H, 4.06; N, 14.90;

Found C, 51.23; H, 4.28; N, 14.90.

5-[1-(4-azabenzimidazolyl)methyl]-1-(4-cyanobenzyl)imidazole hydrochloride

Analysis calculated for formula: $C_{18}H_{14}N_6 \bullet 3.40$ HCl $\bullet$ .60 Et_2O

C, 50.75; H, 4.89; N, 17.41;

Found C, 50.71; H, 4.74; N, 17.34.

1-(4-cyanobenzyl)-5-(2-tetrahydroisoquinolinylmethyl)imidazole hydrochloride

Analysis calculated for formula: $C_{21}H_{20}N_4 \bullet 4.45$ HCl $\bullet$ .80 DMF

C, 51.18; H, 5.52; N, 12.24;

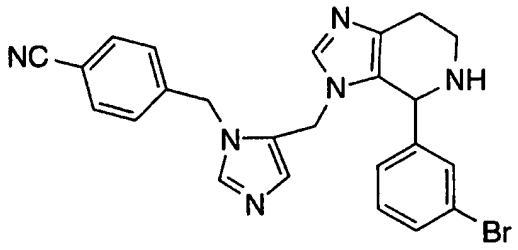
Found C, 51.09; H, 5.25; N, 12.26.

5-(2-benzotriazolylmethyl)-1-(4-cyanobenzyl)imidazole hydrochloride
Analysis calculated for formula: $C_{18}H_{14}N_6 \bullet 1.40$ HCl $\bullet$ .15 Et_2O
C, 59.33; H, 4.52; N, 22.32;
Found C, 59.41; H, 4.38; N, 22.33.

1-(4-cyanobenzyl)-5-(1-isatinylmethyl)imidazole hydrochloride
Analysis calculated for formula: $C_{20}H_{14}N_4O_2 \bullet 1.55$ HCl
C, 60.22; H, 3.93; N, 14.05;
Found C, 60.31; H, 4.16; N, 14.17.

5-[1-(5-azabenzimidazolyl)methyl]-1-(4-cyanobenzyl)imidazole hydrochloride and 5-[3-(5-azabenzimidazolyl)methyl]-1-(4-cyanobenzyl)imidazole hydrochloride
Analysis calculated for formula: $C_{18}H_{14}N_6 \bullet 3.40$ HCl $\bullet$ .60 $CHCl_3$
C, 43.81; H, 3.56; N, 16.48;
Found C, 43.79; H, 3.93; N, 16.17.

EXAMPLE 36



4-{5-[4-(3-Bromophenyl)-4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridin-1-ylmethyl]imidazol-1-ylmethyl}benzonitrile

Step 1: Preparation of 4-(3-bromo-phenyl)-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine

Histamine dihydrochloride (3.68 g, 0.02 mol), KOH (3.36 g, 0.06 mol), and 3-bromobenzaldehyde were dissolved in H_2O (250 mL) and EtOH(100 mL). The reaction mixture was heated for 24 h at 77°C open to the atmosphere. The resulting white precipitate was filtered and dried under vacuum at 40°C to give the title compound.

Step 2: Preparation of 4-(3-bromo-phenyl)-6,7-dihydro-4*H*-imidazo[4,5-*c*]pyridine-1,5-dicarboxylic acid di-*tert*-butyl ester

4-(3-Bromo-phenyl)-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridine (1.0 g, 3.6 mmol), Boc_2O (1.74 g, 7.9 mmol), and Et_3N (1.1 mL, 7.9 mmol) were dissolved in CH_2Cl_2 (35 mL) and stirred overnight at room temperature under Ar. The reaction was washed with H_2O, brine, and dried (Na_2SO_4). Filtration, concentration, and silica gel chromatography (1:6 EtOAc/hexane) yielded the title compound.

Step 3: Preparation of 4-(3-bromo-phenyl)-1,4,6,7-tetrahydro-imidazo[4,5-*c*]pyridine-5-carboxylic acid *tert*-butyl ester

4-(3-Bromophenyl)-6,7-dihydro-4*H*- imidazo[4,5-*c*]pyridine-1,5-dicarboxylic acid di-*tert*-butyl ester (0.879 g, 1.83 mmol) and $Zn(CN)_2$ (0.323 g, 2.75 mmol) were stirred in anh. DMF (30 mL) at 80°C under Ar for 72 h. The solution was concentrated *in vacuo*, partitioned between $CHCl_3$ and sat. $NaHCO_3$ soln, dried ($MgSO_4$), filtered, and concentrated to yield the title compound without further purification.

Step 4: Preparation of 4-(3-bromo-phenyl)-1-[3-(4-cyano-benzyl)-*H*-imidazol-4-ylmethyl]-1,4,6,7-tetrahydro-imidazo[4,5-*c*]pyridine-5-carboxylic acid *tert*-butyl ester

4-(3-Bromo-phenyl)-1,4,6,7-tetrahydro-imidazo[4,5-*c*]pyridine-5-carboxylic acid *tert*-butyl ester (0.160 g, 0.422 mmol) and 5-(chloromethyl)-1-(4-cyanobenzyl)-imidazole hydrochloride, as described in Example 26, Step 1, (0.119 g, 0.444 mmol), were dissolved in DMF (6 mL). NaH (0.62 g, 0.982 mmol) was added, and the reaction mixture was stirred at RT under Ar for 4h. The reaction was concentrated *in vacuo* and partitioned between CH_2Cl_2 and Sat. $NaHCO_3$ soln. The aq. layer was back extracted with CH_2Cl_2 (3X) and the combined CH_2Cl_2 layers dried ($MgSO_4$), filtered and concentrated *in*

vacuo. The residue was chromatographed (2% MeOH/CH_2Cl_2 with NH_4OH) to yield the title compound.

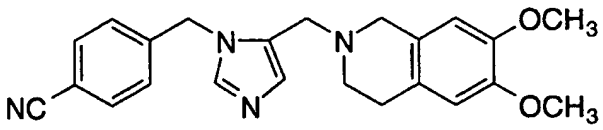
Step 5: Preparation of 4-{5-[4-(3-bromophenyl)-4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridin-1-ylmethyl]imidazol-1-ylmethyl}-benzonitrile

To a solution of 4-(3-bromophenyl)-1-[3-(4-cyanobenzyl)-3*H*-imidazol-4-ylmethyl]-1,4,6,7-tetrahydroimidazo[4,5-*c*]pyridine-5-carboxylic acid *tert*-butyl ester (0.045 g, 0.078 mmol) dissolved in CH_2Cl_2 (5 mL) was added TFA (1 mL) and the reaction mixture was stirred at room temperature under Ar for 2h. The solution was concentrated *in vacuo* and purified using reverse phase liquid chromatography (95/5 -5/95 H_2O/CH_3CN with 0.1% TFA over 60 min, flow rate = 65 mL/min) to yield the title compound.

^{1}H NMR (CD_3OD); δ 8.75 (d, 1H, J=1 Hz), 7.83 (s, 1H), 7.74 (d, 2H, J=8.5Hz), 7.70 (d, 1H, J=8Hz), 7.46 (s, 1H), 7.41 (t, 1H, J=8Hz), 7.28 (d, 1H, J=8Hz), 7.21 (d, 2H, J=8.5Hz), 7.18 (s, 1H), 5.83 (s, 1H), 5.34 (d, 1H, J=16Hz), 5.27 (d, 1H, J=16Hz), 4.99 (d, 1H, J=16Hz), 4.79 (d, 1H, J=16Hz), 3.43 (t, 2H, J=6Hz), 3.12-2.96 (m, 2H).

High resolution MS, $C_{24}H_{21}BrN_5$: Calc MW, 473.1084. Found, 473.1079.

EXAMPLE 37



6,7-Dimethoxy-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)1,2,3,4-tetrahydroisoquinoline

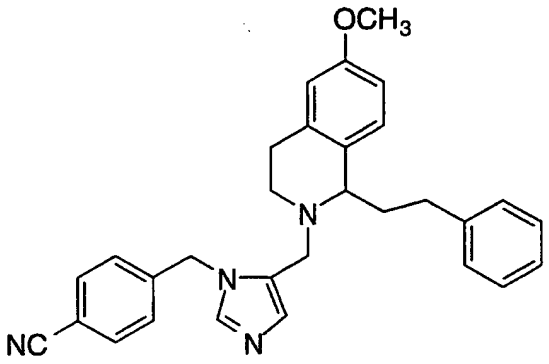
Following the procedure described in Example 1, Step 6 using 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (Aldrich), the title compound was obtained as a colorless gum.

Analysis for $C_{23}H_{24}N_4O_2$•O.10 EtOAc

Calc'd C, 70.74 H, 6.29 N, 14.10

Found C, 70.75 H, 6.21 N, 13.87

EXAMPLE 38



1(R,S)-(2-Phenethyl)-6-methoxy-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

Step 1: Preparation of N-(2-phenethyl) 2-(3-methoxyphenethyl) amine

Following the procedure described in Example 1, Step 6 but using 3-methoxyphenethylamine (2.9 mL, 20 mmol) and 3-phenyl propionyl chloride (6 mL, 40 mmol), the title compound was obtained as a colorless solid, mp. 49-51°C.
FAB ms (M+H) 284.2.

Step 2: Preparation of 1-(2-phenethyl)-6-methoxy-3,4-dihydroisoquinoline

Following the procedure described in Example 25, Step 2 but using the amide from Step 1 (2.83g, 10 mmol) the title compound was obtained as a colorless gum.
FAB ms (M+H) 266.2.

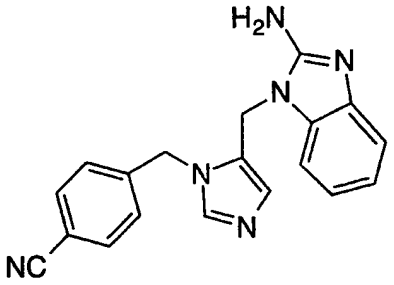
Step 3: Preparation of 1(R,S)-(2-phenethyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline

Following the procedure described in Example 25, Step 3 but using the imine from Step 2 (530 mg, 2 mmol) the title compound was obtained as a colorless gum.
FAB ms (M+H) 268.3.

Step 4: Preparation of 1(R,S)-(2-Phenethyl)-6-methoxy-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

Following the procedure described in Example 1, Step 6 but using the product from Step 3, the title compound was obtained as a colorless gum which was then converted to the bis HCl salt.
FAB ms (M+H) 463.3.
Analysis for $C_{30}H_{30}N_4O \bullet 2HCl \bullet 0.20\ EtOH \bullet 0.70\ HCl$
Calc'd C, 6402, H, 5.99 N, 9.83
Found C, 64.06, H, 6.33 N, 9.77

EXAMPLE 39



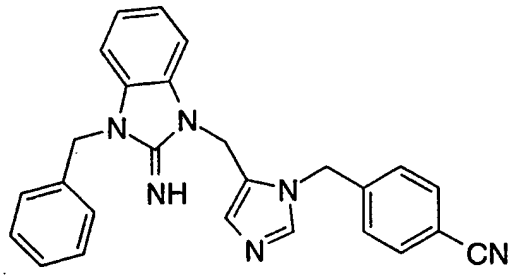
1-(4-Cyanobenzyl)-5-(2-amino-1 -benzimidazolylmethyl)imidazole

The compound described in Example 26, Step 1 [1-(4-cyanobenzyl)-5-(chloromethyl)imidazole hydrochloride] (0.75mmol, 0.20g), 2-aminobenzimidazole (0.90mmol, 0.12g) and diisopropylethylamine (2.25 mmol, 0.29g) were dissolved in acetonitrile and placed in a nitrogen purged sealed tube and warmed at 80°C for 18hr. The precipitate was filtered off to yield 1-(4-cyanobenzyl)-5-(2-amino-1-benzimidazolylmethyl)imidazole.

Structure was confirmed by ^{1}H-NMR-NOE. FAB-MS: calc: 328.4 found: 329.1. Elemental analysis. Calc: C, 67.09; H, 5.19; N, 25.22. Found: C, 67.09; H,4.99; N, 25.26. ^{1}H-NMR (CD_3OD): δ 5.2 (s, 2H), 5.3 (s, 2H), 6.6ppm (d, 2H), 6.9-7.1 (4H), 7.2 (s, 1H), 7.3 (d, 2H), 7.8 (s, 1H).

EXAMPLE 40

1-(4-cyanobenzyl)-5-(2-amino-1-(3-benzyl-2-imino-1-benzimidazolylmethyl)imidazole



The compound described in Example 26, Step 1, 1-(4-cyanobenzyl)-5-(chloromethyl)imidazole hydrochloride (1.0mmol, .234g), 2-amino-1-benzylbenzimidazole (1.0mmol, 0.223g) and diisopropylethylamine (2.25mmol, 0.29g) were dissolved in acetonitrile and placed in a nitrogen purged sealed tube and warmed at 80°C for 18 hours. The acetonitrile was removed under vacuum and the residue was partitioned between ethylacetate/water. The ethyl acetate layer was separated and the aqueous layer extracted. The combined extracts were washed with water, brine and dried $MgSO_4$. The solvent was removed and a crude mixture obtained. The mixture was purified on C_{18} preparative HPLC column to yield the title compound.

Structure confirmed by ^{1}H-NMR-FAB-HRMS
^{1}H NMR (CD_3OD): 5.35 ppm (s, 2H), 5.63ppm (s, 2H), 5.73ppm (s, 2H), 7.29-7.41ppm (m, 11H), 7.66ppm (d, 2H), 7.75ppm (s, 1H), 9.15ppm (s, 1H).
Theoretical HRMS:419.1979; Measured HRMS:419.1983,

EXAMPLE 41

In vitro inhibition of ras farnesyl transferase

Assays of farnesyl-protein transferase. Partially purified bovine FPTase and Ras peptides (Ras-CVLS (SEQ.ID.NO.: 11), Ras-CVIM (SEQ.ID.NO.: 1) and Ras-CAIL (SEQ.ID.NO.: 12)) were prepared as described by Schaber et al., J. Biol. Chem. 265:14701-14704 (1990), Pompliano, et al., Biochemistry 31:3800 (1992) and Gibbs et al., PNAS U.S.A. 86:6630-6634 (1989), respectively. Bovine FPTase was assayed in a volume of 100 ml containing 100 mM *N*-(2-hydroxy ethyl) piperazine-*N'*-(2-ethane sulfonic acid) (HEPES), pH 7.4, 5 mM $MgCl_2$, 5 mM dithiothreitol (DTT), 100 mM [^{3}H]-farnesyl diphosphate ([^{3}H]-FPP; 740 CBq/mmol, New England Nuclear), 650 nM Ras-CVLS and 10 mg/ml FPTase at 31°C for 60 min. Reactions were initiated with FPTase and stopped with 1 ml of 1.0 M HCL in ethanol. Precipitates were collected onto filter-mats using a TomTec Mach II cell harvestor, washed with 100% ethanol, dried and counted in an LKB b-plate counter. The assay was linear with respect to both substrates, FPTase levels and time; less than 10% of the [^{3}H]-FPP was utilized during the reaction period. Purified compounds were dissolved in 100% dimethyl sulfoxide (DMSO) and were diluted 20-fold into the assay. Percentage inhibition is measured by the amount of incorporation of radioactivity in the presence of the test compound when compared to the amount of incorporation in the absence of the test compound.

Human FPTase was prepared as described by Omer et al., Biochemistry 32:5167-5176 (1993). Human FPTase activity was assayed as described above with the exception that 0.1% (w/v) polyethylene glycol 20,000, 10 mM $ZnCl_2$ and 100 nM Ras-CVIM were added to the reaction mixture. Reactions were performed for 30 min., stopped with 100 ml of 30% (v/v) trichloroacetic acid (TCA) in ethanol and processed as described above for the bovine enzyme.

The compounds of the instant invention described in the above Examples were tested for inhibitory activity against human

FPTase by the assay described above and were found to have IC_{50} of <50 μM.

EXAMPLE 42

Modified *In vitro* GGTase inhibition asssay

The modified geranylgeranyl-protein transferase inhibition assay is carried out at room temperature. A typical reaction contains (in a final volume of 50 mL): [^{3}H]geranylgeranyl diphosphate, biotinylated Ras peptide, 50 mM HEPES, pH 7.5, a modulating anion (for example 10 mM glycerophosphate or 5mM ATP), 5 mM $MgCl_2$, 10 mM $ZnCl_2$, 0.1% PEG (15-20,000), 2 mM dithiothreitol, and geranylgeranyl-protein transferase type I(GGTase). The GGTase-type I enzyme employed in the assay is prepared as described in U.S. Pat. No. 5,470,832, incorporated by reference. The Ras peptide is derived from the K4B-Ras protein and has the following sequence: biotinyl-GKKKKKKSKTKCVIM (single amino acid code) (SEQ.ID.NO.: 13). Reactions are initiated by the addition of GGTase and stopped at timed intervals (typically 15 min) by the addition of 200 mL of a 3 mg/mL suspension of streptavidin SPA beads (Scintillation Proximity Assay beads, Amersham) in 0.2 M sodium phosphate, pH 4, containing 50 mM EDTA, and 0.5% BSA. The quenched reactions are allowed to stand for 2 hours before analysis on a Packard TopCount scintillation counter.

For inhibition studies, assays are run as described above, except inhibitors are prepared as concentrated solutions in 100% dimethyl sulfoxide and then diluted 25-fold into the enzyme assay mixture. IC_{50} values are determined with Ras peptide near K_M concentrations. Enzyme and nonsaturating substrate conditions for inhibitor IC_{50} determinations are as follows: 75 pM GGTase-I, 1.6 mM Ras peptide, 100 nM geranylgeranyl diphosphate.

EXAMPLE 43

Cell-based *in vitro* ras prenylation assay

The cell lines used in this assay consist of either Rat1 or NIH3T3 cells transformed by either viral H-ras; an N-ras chimeric gene in which the C-terminal hypervariable region of viral-H-ras was substituted with the corresponding region from the N-ras gene; or ras-CVLL, a viral-H-ras mutant in which the C-terminal exon encodes leucine instead of serine, making the encoded protein a substrate for geranylgeranylation by GGTase-I. The assay can also be performed using cell lines transformed with human H-ras, N-ras or K4B-ras. The assay is performed essentially as described in DeClue, J.E. et al., Cancer Research 51:712-717, (1991). Cells in 10 cm dishes at 50-75% confluency are treated with the test compound(s) (final concentration of solvent, methanol or dimethyl sulfoxide, is 0.1%). After 4 hours at 37°C, the cells are labelled in 3 ml methionine-free DMEM supplemented with 10% regular DMEM, 2% fetal bovine serum, 400 mCi[^{35}S]methionine (1000 Ci/mmol) and test compound(s). Cells treated with lovastatin, a compound that blocks Ras processing in cells by inhibiting the rate-limiting step in the isoprenoid biosynthetic pathway (Hancock, J.F. et al. *Cell*, 57:1167 (1989); DeClue, J.E. et al. *Cancer Res.*, 51:712 (1991); Sinensky, M. et al. *J. Biol. Chem.*, 265:19937 (1990)), serve as a positive control in this assay. After an additional 20 hours, the cells are lysed in 1 ml lysis buffer (1% NP40/20 mM HEPES, pH 7.5/5 mM $MgCl_2$/1mM DTT/10 mg/ml aprotinen/2 mg/ml leupeptin/2 mg/ml antipain/0.5 mM PMSF) and the lysates cleared by centrifugation at 100,000 x g for 45 min. Alternatively, four hours after the additon of the labelling media, the media is removed, the cells washed, and 3 ml of media containing the same or a different test compound added. Following an additional 16 hour incubation, the lysis is carried out as above. Aliquots of lysates containing equal numbers of acid-precipitable counts are bought to 1 ml with IP buffer (lysis buffer lacking DTT) and immunoprecipitated with the ras-specific monoclonal antibody Y13-259 (Furth, M.E. et al., J. Virol. 43:294-304, (1982)). Following a 2 hour antibody incubation at 4°C, 200 ml of a 25%

suspension of protein A-Sepharose coated with rabbit anti rat IgG is added for 45 min. The immunoprecipitates are washed four times with IP buffer (20 nM HEPES, pH 7.5/1 mM EDTA/1% Triton X-100.0.5% deoxycholate/0.1%/SDS/0.1 M NaCl) boiled in SDS-PAGE sample buffer and loaded on 13% acrylamide gels. When the dye front reached the bottom, the gel is fixed, soaked in Enlightening, dried and autoradiographed. The intensities of the bands corresponding to prenylated and nonprenylated Ras proteins are compared to determine the percent inhibition of prenyl transfer to protein.

EXAMPLE 44

Cell-based *in vitro* anchorage independent growth assay (SALSA)

SALSA (Soft Agar-Like Surrogate Assay) measures the inhibition of anchorage-independent growth by prenyl-transferase inhibitors. Only transformed cells are able to grow anchorage-independently in the SALSA format. Additionally, cells growing in the SALSA format grow in clumps, resembling the colonies formed in soft agar. SALSA may been used to measure the growth inhibition by prenyl-transferase inhibitors in a variety of transformed cell lines, including Rat1 fibroblasts transformed with viral-H-ras (H-ras/rat1), as well as a panel of human tumor cell lines (HTL's).

SALSA is performed in 96-well plates that are coated with a thin film of the polymer, PolyHEMA (Poly(2-hydroxyethyl methacrylate)), which prevents cells from attaching to the plate. Rat1 fibroblast cells transformed with v-Ha-ras (this cell line has been deposited in the ATCC on August 19, 1997 under the terms of the Budapest convention and has been given a designation of ATCC CRL 12387) are seeded at 5000 cells/well, grown for 4 hr, then vehicle or half-log dilutions of test compound (in either an 8 or 12 point titration) are added. The cells are then grown for 6 days at 37 degrees, without changing the growth media or adding fresh compound. At day 6, cell growth is assessed via a colorimetric assay that measures the cleavage of the tetrazolium dye, MTT, to an insoluble purple formazan, a reaction dependent upon mitochondrial dehydrogenases. At day 6, the cells are

incubated for 4 hr with 0.5 mg/ml MTT, and then SDS is added to 9% w/v to lyse the cells and solubilize the insoluble MTT-formazan. The amount of MTT metabolism is quantitated via spectrophotometric detection at 570 nM. Dose-inhibition curves and IC_{50}'s are determined.

EXAMPLE 45

Construction of SEAP reporter plasmid pDSE100

The SEAP reporter plasmid, pDSE100 was constructed by ligating a restriction fragment containing the SEAP coding sequence into the plasmid pCMV-RE-AKI. The SEAP gene is derived from the plasmid pSEAP2-Basic (Clontech, Palo Alto, CA). The plasmid pCMV-RE-AKI was constructed by Deborah Jones (Merck) and contains 5 sequential copies of the 'dyad symmetry response element' cloned upstream of a 'CAT-TATA' sequence derived from the cytomegalovirus immediate early promoter. The plasmid also contains a bovine growth hormone poly-A sequence.

The plasmid, pDSE100 was constructed as follows. A restriction fragment encoding the SEAP coding sequence was cut out of the plasmid pSEAP2-Basic using the restriction enzymes EcoR1 and HpaI. The ends of the linear DNA fragments were filled in with the Klenow fragment of E. coli DNA Polymerase I. The 'blunt ended' DNA containing the SEAP gene was isolated by electrophoresing the digest in an agarose gel and cutting out the 1694 base pair fragment. The vector plasmid pCMV-RE-AKI was linearized with the restriction enzyme Bgl-II and the ends filled in with Klenow DNA Polymerase I. The SEAP DNA fragment was blunt end ligated into the pCMV-RE-AKI vector and the ligation products were transformed into DH5-alpha E. coli cells (Gibco-BRL). Transformants were screened for the proper insert and then mapped for restriction fragment orientation. Properly oriented recombinant constructs were sequenced across the cloning junctions to verify the correct sequence. The resulting plasmid contains the SEAP coding sequence downstream of the DSE and CAT-TATA promoter elements and upstream of the BGH poly-A sequence.

Cloning of a Myristylated viral-H-*ras* expression plasmid

A DNA fragment containing viral-H-*ras* can be PCRed from plasmid "H-1" (Ellis R. et al. J. Virol. **36**, 408, 1980) using the following oligos.

Sense strand:
5'TCTCCTCGAGGCCACCATGGGGAGTAGCAAGAGCAAGCCTAA GGACCCCAGCCAGCGCCGGATGACAGAATACAAGCTTGTGGTG G 3'. (SEQ.ID.NO.: 14)

Antisense: 5'CACATCTAGATCAGGACAGCACAGACTTGCAGC 3'. (SEQ.ID.NO.: 15)

A sequence encoding the first 15 aminoacids of the v-src gene, containing a myristylation site, is incorporated into the sense strand oligo. The sense strand oligo also optimizes the 'Kozak' translation initiation sequence immediately 5' to the ATG start site.To prevent prenylation at the viral-*ras* C-terminus, cysteine 186 would be mutated to a serine by substituting a G residue for a C residue in the C-terminal antisense oligo. The PCR primer oligos introduce an XhoI site at the 5' end and a XbaI site at the 3'end. The XhoI-XbaI fragment can be ligated into the mammalian expression plasmid pCI (Promega) cut with XhoI and XbaI. This results in a plasmid in which the recombinant myr-viral-H-ras gene is constitutively transcribed from the CMV promoter of the pCI vector.

Cloning of a viral-H-*ras*-CVLL expression plasmid

A viral-H-*ras* clone with a C-terminal sequence encoding the amino acids CVLL can be cloned from the plasmid "H-1" (Ellis R. et al. J. Virol. **36**, 408, 1980) by PCR using the following oligos.

Sense strand:
5'TCTCCTCGAGGCCACCATGACAGAATACAAGCTTGTGGTGG-3' (SEQ.ID.NO.: 16)

Antisense strand:
5'CACTCTAGACTGGTGTCAGAGCAGCACACACTTGCAGC-3' (SEQ.ID.NO.: 17)

The sense strand oligo optimizes the 'Kozak' sequence and adds an XhoI site. The antisense strand mutates serine 189 to leucine and adds an XbaI site. The PCR fragment can be trimmed with XhoI and XbaI and ligated into the XhoI-XbaI cut vector pCI (Promega). This results in a plasmid in which the mutated viral-H-*ras*-CVLL gene is constitutively transcribed from the CMV promoter of the pCI vector.

Cloning of c-H-*ras*-Leu61 expression plasmid

The human c-H-*ras* gene can be PCRed from a human cerebral cortex cDNA library (Clontech) using the following oligonucleotide primers.

Sense strand:
5'-GAGAGAATTCGCCACCATGACGGAATATAAGCTGGTGG-3' (SEQ.ID.NO.: 18)

Antisense strand:
5'-GAGAGTCGACGCGTCAGGAGAGCACACACTTGC-3' (SEQ.ID.NO.: 19)

The primers will amplify a c-H-*ras* encoding DNA fragment with the primers contributing an optimized 'Kozak' translation start sequence, an EcoRI site at the N-terminus and a Sal I stite at the C-terminal end. After trimming the ends of the PCR product with EcoRI and Sal I, the c-H-ras fragment can be ligated ligated into an EcoRI -Sal I cut mutagenesis vector pAlter-1 (Promega). Mutation of glutamine-61 to a

leucine can be accomplished using the manufacturer's protocols and the following oligonucleotide:

5'-CCGCCGGCCTGGAGGAGTACAG-3' (SEQ.ID.NO.: 20)

After selection and sequencing for the correct nucleotide substitution, the mutated c-H-*ras*-Leu61 can be excised from the pAlter-1 vector, using EcoRI and Sal I, and be directly ligated into the vector pCI (Promega) which has been digested with EcoRI and Sal I. The new recombinant plasmid will constitutively transcribe c-H-*ras*-Leu61 from the CMV promoter of the pCI vector.

Cloning of a c-N-*ras*-Val-12 expression plasmid

The human c-N-*ras* gene can be PCRed from a human cerebral cortex cDNA library (Clontech) using the following oligonucleotide primers.

Sense strand:
5'-GAGAGAATTCGCCACCATGACTGAGTACAAACTGGTGG-3'
(SEQ.ID.NO.:21)

Antisense strand:
5'-GAGAGTCGACTTGTTACATCACCACACATGGC-3'
(SEQ.ID.NO.: 22)

The primers will amplify a c-N-*ras* encoding DNA fragment with the primers contributing an optimized 'Kozak' translation start sequence, an EcoRI site at the N-terminus and a Sal I stite at the C-terminal end. After trimming the ends of the PCR product with EcoRI and Sal I, the c-N-ras fragment can be ligated into an EcoRI -Sal I cut mutagenesis vector pAlter-1 (Promega). Mutation of glycine-12 to a valine can be accomplished using the manufacturer's protocols and the following oligonucleotide:

5'-GTTGGAGCAGTTGGTGTTGGG-3' (SEQ.ID.NO.: 23)

After selection and sequencing for the correct nucleotide substitution, the mutated c-N-*ras*-Val-12 can be excised from the pAlter-1 vector, using EcoRI and Sal I, and be directly ligated into the vector pCI (Promega) which has been digested with EcoRI and Sal I. The new recombinant plasmid will constitutively transcribe c-N-*ras*-Val-12 from the CMV promoter of the pCI vector.

Cloning of a c-K-*ras*-Val-12 expression plasmid

The human c-K-*ras* gene can be PCRed from a human cerebral cortex cDNA library (Clontech) using the following oligonucleotide primers.

Sense strand:
5'-GAGAGGTACCGCCACCATGACTGAATATAAACTTGTGG-3'
(SEQ.ID.NO.: 24)

Antisense strand:
5'-CTCTGTCGACGTATTTACATAATTACACACTTTGTC-3'
(SEQ.ID.NO.: 25)

The primers will amplify a c-K-*ras* encoding DNA fragment with the primers contributing an optimized 'Kozak' translation start sequence, a KpnI site at the N-terminus and a Sal I stite at the C-terminal end. After trimming the ends of the PCR product with Kpn I and Sal I, the c-K-*ras* fragment can be ligated into a KpnI -Sal I cut mutagenesis vector pAlter-1 (Promega). Mutation of cysteine-12 to a valine can be accomplished using the manufacturer's protocols and the following oligonucleotide:

5'-GTAGTTGGAGCTGTTGGCGTAGGC-3' (SEQ.ID.NO.: 26)

After selection and sequencing for the correct nucleotide substitution, the mutated c-K-*ras*-Val-12 can be excised from the pAlter-1 vector, using KpnI and Sal I, and be directly ligated into the vector pCI (Promega) which has been digested with KpnI and Sal I. The new recombinant plasmid will constitutively transcribe c-K-*ras*-Val-12 from the CMV promoter of the pCI vector.

SEAP assay

Human C33A cells (human epitheial carcenoma - ATTC collection) are seeded in 10cm tissue culture plates in DMEM + 10% fetal calf serum + 1X Pen/Strep + 1X glutamine + 1X NEAA. Cells are grown at 37°C in a 5% CO_2 atmosphere until they reach 50 -80% of confluency.

The transient transfection is performed by the $CaPO_4$ method (Sambrook et al., 1989). Thus, expression plasmids for H-*ras*, N-*ras*, K-*ras*, Myr-*ras* or H-*ras*-CVLL are co-precipitated with the DSE-SEAP reporter construct. For 10cm plates 600ml of $CaCl_2$-DNA solution is added dropwise while vortexing to 600ml of 2X HBS buffer to give 1.2ml of precipitate solution (see recipes below). This is allowed to sit at room temperature for 20 to 30 minutes. While the precipitate is forming, the media on the C33A cells is replaced with DMEM (minus phenol red; Gibco cat. # 31053-028)+ 0.5% charcoal stripped calf serum + 1X (Pen/Strep, Glutamine and nonessential aminoacids). The $CaPO_4$-DNA precipitate is added dropwise to the cells and the plate rocked gently to distribute. DNA uptake is allowed to proceed for 5-6 hrs at 37°C under a 5% CO_2 atmosphere.

Following the DNA incubation period, the cells are washed with PBS and trypsinized with 1ml of 0.05% trypsin. The 1 ml of trypsinized cells is diluted into 10ml of phenol red free DMEM + 0.2% charcoal stripped calf serum + 1X (Pen/Strep, Glutamine and NEAA). Transfected cells are plated in a 96 well microtiter plate (100ml/well) to which drug, diluted in media, has already been added in a volume of 100ml. The final volume per well is 200ml with each drug concentration repeated in triplicate over a range of half-log steps.

Incubation of cells and drugs is for 36 hrs at 37° under CO_2. At the end of the incubation period, cells are examined microscopically for evidence of cell distress. Next, 100ml of media containing the secreted alkaline phosphatase is removed from each well and transferred to a microtube array for heat treatment at 65°C for 1 hr to inactivate endogenous alkaline phosphatases (but not the heat stable secreted phosphatase).

The heat treated media is assayed for alkaline phosphatase by a luminescence assay using the luminescence reagent CSPD® (Tropix, Bedford, Mass.). A volume of 50 ml media is combinRased with 200 ml of CSPD cocktail and incubated for 60 minutes at room temperature. Luminesence is monitored using an ML2200 microplate luminometer (Dynatech). Luminescence reflects the level of activation of the fos reporter construct stimulated by the transiently expressed protein.

<u>DNA-$CaPO_4$ precipitate for 10cm. plate of cells</u>

Ras expression plasmid (1mg/ml)	10ml
DSE-SEAP Plasmid (1mg/ml)	2ml
Sheared Calf Thymus DNA (1mg/ml)	8ml
2M $CaCl_2$	74ml
dH_2O	506ml

<u>2X HBS Buffer</u>

280mM NaCl
10mM KCl
1.5mM Na_2HPO_4 $2H_2O$
12mM dextrose
50mM HEPES
Final pH = 7.05

Luminesence Buffer (26ml)

Assay Buffer	20ml
Emerald Reagent™ (Tropix)	2.5ml
100mM homoarginine	2.5ml
CSPD Reagent® (Tropix)	1.0ml

Assay Buffer
Add 0.05M Na_2CO_3 to 0.05M $NaHCO_3$ to obtain pH 9.5. Make 1mM in $MgCl_2$

EXAMPLE 46

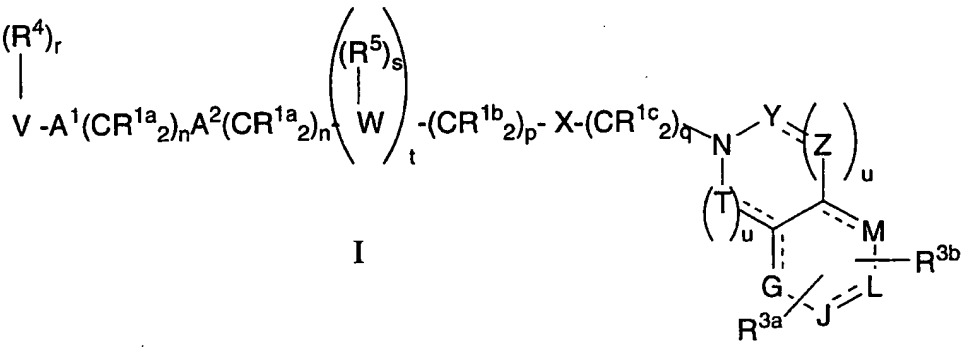
In vivo tumor growth inhibition assay (nude mouse)

In vivo efficacy as an inhibitor of the growth of cancer cells may be confirmed by several protocols well known in the art. Examples of such *in vivo* efficacy studies are described by N. E. Kohl et al. (*Nature Medicine*, 1:792-797 (1995)) and N. E. Kohl et al. (*Proc. Nat. Acad. Sci. U.S.A.*, 91:9141-9145 (1994)).

Rodent fibroblasts transformed with oncogenically mutated human Ha-*ras* or Ki-*ras* (10^6 cells/animal in 1 ml of DMEM salts) are injected subcutaneously into the left flank of 8-12 week old female nude mice (Harlan) on day 0. The mice in each oncogene group are randomly assigned to a vehicle, compound or combination treatment group. Animals are dosed subcutaneously starting on day 1 and daily for the duration of the experiment. Alternatively, the farnesyl-protein transferase inhibitor may be administered by a continuous infusion pump. Compound, compound combination or vehicle is delivered in a total volume of 0.1 ml. Tumors are excised and weighed when all of the vehicle-treated animals exhibited lesions of 0.5 - 1.0 cm in diameter, typically 11-15 days after the cells were injected. The average weight of the tumors in each treatment group for each cell line is calculated.

WHAT IS CLAIMED IS:

1. A compound which inhibits farnesyl-protein transferase of the formula I:



I

wherein:

R^{1a}, R^{1b} and R^{1c} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) C_1-C_6 alkyl unsubstituted or substituted by unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)$-NR^8-,

provided that R^{1a} is not unsubstituted or substituted imidazolyl;

R^{2a}, $R^{2b'}$ and $R^{2b''}$ are independently hydrogen, NH_2 or -$(CR^{11}{}_2)_vA^3(CR^{12}{}_2)_wR^{13}$; or

$R^{2b'}$ and $R^{2b''}$ are combined as O;

R^{3a} and R^{3b} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-$C(NR^8)$-, CN, NO_2, $R^8C(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-$C(NR^8)$-, CN, $R^8C(O)$-, N_3, $-N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^4 is independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $R^8{}_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NH$-, CN, H_2N-$C(NH)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^8OC(O)NH$-,

provided that R^4 is not unsubstituted or substituted imidazolyl;

R^5 is independently selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-C-(NR^8)-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

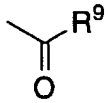
c) C_1-C_6 alkyl, unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, $(R^8)_2N$-C(NR^8)-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

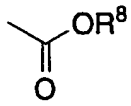
R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

R^{10} is selected from: H; $R^8C(O)$-; $R^9S(O)_m$-; unsubstituted or substituted C_{1-4} alkyl, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted heterocycle, unsubstituted or substituted aryl, substituted aroyl, unsubstituted or substituted heteroaroyl, substituted arylsulfonyl, unsubstituted or substituted heteroarylsulfonyl, wherein the substituted group is substituted with one or two substituents selected from:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,

e)  ,

f)  ,

g) $-S(O)_mR^9$,

h) $N(R^8)_2$, or
i) C_{3-6} cycloalkyl;

R^{11} and R^{12} are independently selected from:
a) hydrogen,
b) C_1-C_6 alkyl unsubstituted or substituted by C_2-C_{20} alkenyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, N_3, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-,
c) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_{20} alkenyl, halogen, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and
d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C_3-C_{10} cycloalkyl;

R^{13} is selected from:
a) hydrogen,
b) substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_{20} alkenyl, C_2-C_{20} alkynyl, C_1-C_{20} perfluoroalkyl, allyloxy, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $R^8{}_2N$-$C(NR^8)$-, $R^8C(O)$-, N_3, $-N(R^8)_2$, $(R^9)_2NC(O)$- or $R^9OC(O)NR^8$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_{20} alkenyl, C_2-C_{20} alkynyl, C_2-C_{20} perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NH$-, CN, H_2N-$C(NH)$-, $R^8C(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NH$-;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^8-, -NR^8C(O)-, O, -N(R^8)-, -S(O)$_2$N(R^8)-, -N(R^8)S(O)$_2$-, or -S(O)$_m$;

A^3 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, -S(O)$_2$N(R^{10})-, -N(R^{10})S(O)$_2$-, or S(O)$_m$;

G, J, L and M are independently selected from: CH_y or N;

T is selected from: N, $CR^{2b'}$ or $CR^{2b'}R^{2b''}$;

V is selected from:

a) hydrogen,
b) heterocycle,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is S(O)$_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is S(O)$_m$;
and provided that V is not imidazolyl;

W is a heterocycle;

X is a bond, -S(O)$_m$-, O or -C(=O)-;

Y is selected from: CR^{2a}, C=O, C=NH or N;

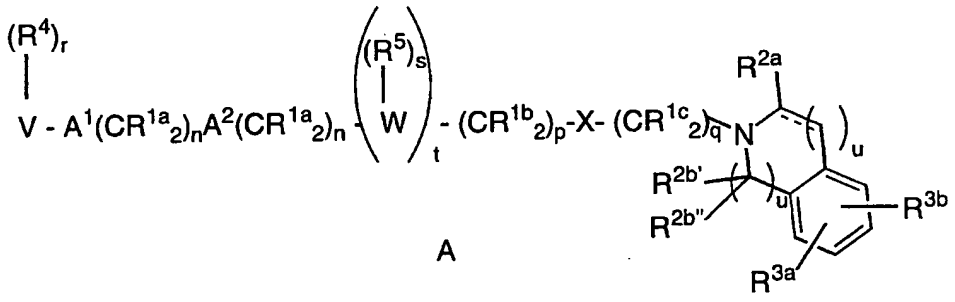
Z is selected from: CR^{2a}, C=O or N;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4;
q is 0, 1, 2, 3 or 4, provided that q is not 0 or 1 if X is O;
r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 1 or 2;
t is independently 0 or 1;
u is independently 0,1 or 2;
v is 0, 1, 2, 3 or 4, provided that v is not 0 when A^3 is $-NR^{10}C(O)-$, O, $-N(R^{10})-$, $-S(O)_2N(R^{10})-$, $-N(R^{10})S(O)_2-$, or $S(O)_m$;
w is 0, 1, 2, 3 or 4; and
y is 1 or 2;
the dashed lines represent optional double bonds;

or an optical isomer or a pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1 which inhibits farnesyl-protein transferase of the formula A:



A

wherein:
R^{1a}, R^{1b} and R^{1c} are independently selected from:

a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_m-$, $R^8C(O)NR^8-$, CN, NO_2,

$(R^8)_2N$-C(NR^8)-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) C_1-C_6 alkyl unsubstituted or substituted by unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, $(R^8)_2N$-C(NR^8)-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)$-NR^8-,

provided that R^{1a} is not unsubstituted or substituted imidazolyl;

R^{2a}, $R^{2b'}$ and $R^{2b''}$ are independently hydrogen or -$(CR^{11}{}_2)_vA^3(CR^{12}{}_2)_wR^{13}$; or
$R^{2b'}$ and $R^{2b''}$ are combined as O;

R^{3a} and R^{3b} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-C(NR^8)-, CN, NO_2, $R^8C(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-C(NR^8)-, CN, $R^8C(O)$-, N_3, -$N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^4 is independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $R^8{}_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NH$-, CN, H_2N-$C(NH)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^8OC(O)NH$-,

provided that R^4 is not unsubstituted or substituted imidazolyl;

R^5 is independently selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-C-(NR^8)-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl, unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

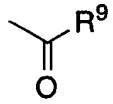
R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

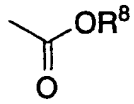
R^9 is independently selected from C_1-C_6 alkyl and aryl;

R^{10} is selected from: H; $R^8C(O)$-; $R^9S(O)_m$-; unsubstituted or substituted C_{1-4} alkyl, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted heterocycle, unsubstituted or substituted aryl, substituted aroyl, unsubstituted or substituted heteroaroyl, substituted arylsulfonyl, unsubstituted or substituted heteroarylsulfonyl,

wherein the substituted group is substituted with one or two substituents selected from:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,

e)  ,

f)  ,

g) $-S(O)_mR^9$,

h) $N(R^8)_2$, or
i) C_{3-6} cycloalkyl;

R^{11} and R^{12} are independently selected from:

a) hydrogen,
b) C_1-C_6 alkyl unsubstituted or substituted by C_2-C_{20} alkenyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, N_3, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-,
c) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_{20} alkenyl, halogen, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and
d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C_3-C_{10} cycloalkyl;

R^{13} is selected from:

a) hydrogen,

b) substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_{20} alkenyl, C_2-C_{20} alkynyl, C_1-C_{20} perfluoroalkyl, allyloxy, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $R^8{}_2N$-$C(NR^8)$-, $R^8C(O)$-, N_3, -$N(R^8)_2$, $(R^9)_2NC(O)$- or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_{20} alkenyl, C_2-C_{20} alkynyl, C_2-C_{20} perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NH$-, CN, H_2N-$C(NH)$-, $R^8C(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NH$-;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^8$-, -$NR^8C(O)$-, O, -$N(R^8)$-, -$S(O)_2N(R^8)$-, -$N(R^8)S(O)_2$-, or -$S(O)_m$;

A^3 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

V is selected from:

a) hydrogen,

b) heterocycle,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

and provided that V is not imidazolyl;

W is a heterocycle;

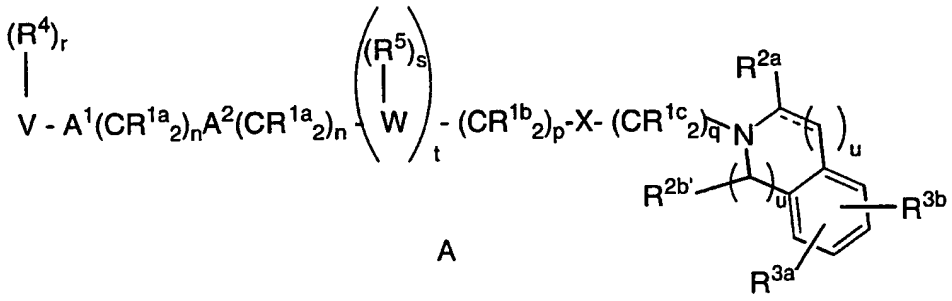
X is a bond, -S(O)$_m$-, O or -C(=O)-;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
q is 0, 1, 2, 3 or 4, provided that q is not 0 or 1 if X is O;
r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 1 or 2;
t is 0 or 1;
u is independently 0,1 or 2;
v is 0, 1, 2, 3 or 4, provided that v is not 0 when A^3 is -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or S(O)$_m$;
w is 0, 1, 2, 3 or 4; and

the dashed lines represent optional double bonds;

or an optical isomer or a pharmaceutically acceptable salt thereof.

3. The compound according to Claim 2 which inhibits farnesyl-protein transferase of the formula A:



A

wherein:

R^{1a} and R^{1c} are independently selected from: hydrogen, C_3-C_{10} cycloalkyl, R^8O-, -$N(R^8)_2$, F or C_1-C_6 alkyl;

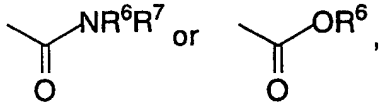
R^{1b} is independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_6 cycloalkyl, R^8O-, -$N(R^8)_2$ or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by unsubstituted or substituted aryl, heterocycle, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, R^8O-, or -$N(R^8)_2$;

R^{2a} and $R^{2b'}$ are independently selected from: H; C_1-C_6 alkyl,



R^{3a} and R^{3b} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-$C(NR^8)$-, CN, NO_2, $R^8C(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-$C(NR^8)$-, CN, $R^8C(O)$-, N_3, -$N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^4 is independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^5 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^6 and R^7 are independently selected from:

H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with one or two:

a) C_{1-4} alkoxy,

b) halogen, or

c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle,

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^8-, O, -N(R^8)-, or -S(O)$_m$;

V is selected from:

a) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, indolyl, quinolinyl, isoquinolinyl, and thienyl, and

b) aryl;

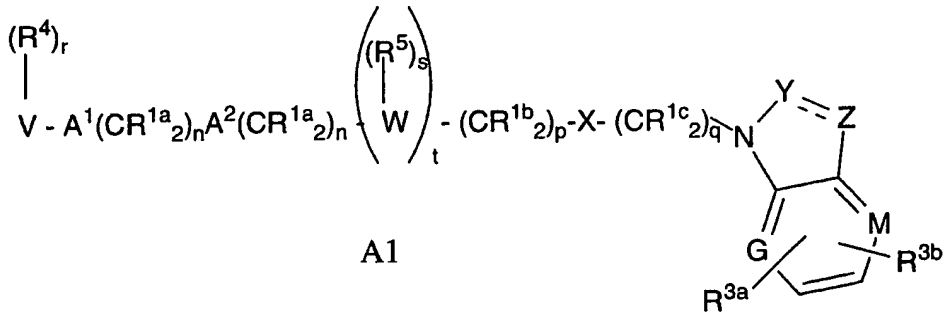
W is a heterocycle selected from pyrrolidinyl, triazolyl, imidazolyl, pyridinyl, thiazolyl, indolyl, quinolinyl, or isoquinolinyl;

X is a bond, -S(O)$_m$-, O or -C(=O)-;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 1, 2 or 3;
q is 0, 1 or 2, provided that q is not 0 or 1 if X is O;
r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 1 or 2;
t is 1; and
u is independently 0 or 1;

or an optical isomer or a pharmaceutically acceptable salt thereof.

4. The compound according to Claim 1 which inhibits farnesyl-protein transferase of the formula A1:



A1

wherein

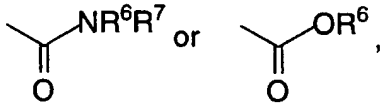
R^{1a} and R^{1c} are independently selected from: hydrogen, C_3-C_{10} cycloalkyl, R^8O-, -$N(R^8)_2$, F or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_6 cycloalkyl, R^8O-, -$N(R^8)_2$ or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by unsubstituted or substituted aryl, heterocycle, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, R^8O-, or -$N(R^8)_2$;

R^{2a} is selected from: H; C_1-C_6 alkyl, NH_2  ,

R^{3a} and R^{3b} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-$C(NR^8)$-, CN, NO_2, $R^8C(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-$C(NR^8)$-, CN, $R^8C(O)$-, N_3, -$N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^4 is independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^5 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^6 and R^7 are independently selected from:

H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with one or two:

a) C_{1-4} alkoxy,

b) halogen, or
c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle,

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^8-, -NR^8C(O)-, O, -N(R^8)-, -$S(O)_2N(R^8)$-, -N(R^8)$S(O)_2$-, or -$S(O)_m$;

G and M are independently selected from: CH_y or N;

V is selected from:
a) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, indolyl, quinolinyl, isoquinolinyl, and thienyl, and
b) aryl;

W is a heterocycle selected from pyrrolidinyl, triazolyl, imidazolyl, pyridinyl, thiazolyl, indolyl, quinolinyl, or isoquinolinyl;

X is a bond, -$S(O)_m$-, O or -C(=O)-;

Y is selected from: CR^{2a}, C=O, C=NH or N;

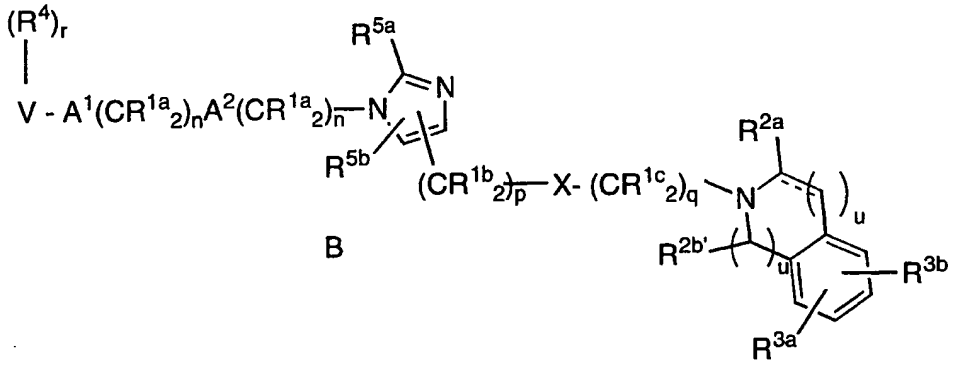
Z is selected from: CR^{2a}, C=O or N;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 1, 2 or 3;
q is 0, 1 or 2, provided that q is not 0 or 1 if X is O;

r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 1 or 2;
t is 1; and
y is 1 or 2;

or an optical isomer or a pharmaceutically acceptable salt thereof.

5. The compound according to Claim 2 which inhibits farnesyl-protein transferase of the formula B:



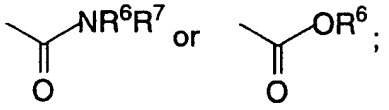
B

wherein:

R^{1a} and R^{1c} are independently selected from: hydrogen, C_3-C_{10} cycloalkyl, R^8O-, -$N(R^8)_2$, F or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, R^8O-, -$N(R^8)_2$, F or C_2-C_6 alkenyl,
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, R^8O- and -$N(R^8)_2$;

R^{2a} and $R^{2b'}$ are independently selected from selected from: H; C_1-C_6 alkyl,  ;

R^{3a} and R^{3b} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-$C(NR^8)$-, CN, NO_2, $R^8C(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-$C(NR^8)$-, CN, $R^8C(O)$-, N_3, $-N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^4 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^{5a} and R^{5b} are independently hydrogen, C_1-C_6 alkyl, cyclopropyl, trifluoromethyl and halogen;

R^6 and R^7 are independently selected from:
H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with one or two:
a) C_{1-4} alkoxy,
b) halogen, or
c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^8-, O, -$N(R^8)$-, or -$S(O)_m$;

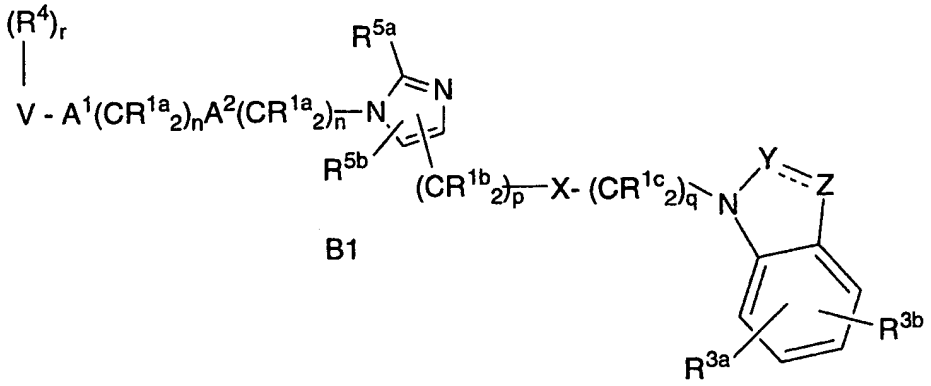
V is selected from:
a) hydrogen,
b) heterocycle selected from pyrrolidinyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl, and
provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

X is a bond, -$S(O)_m$-, O or -C(=O)-;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
q is 0, 1 or 2, provided that q is not 0 or 1 if X is O;
r is 0 to 5, provided that r is 0 when V is hydrogen; and
u is independently 0 or 1;

or an optical isomer or pharmaceutically acceptable salt thereof.

6. The compound according to Claim 1 which inhibits farnesyl-protein transferase of the formula B1:



B1

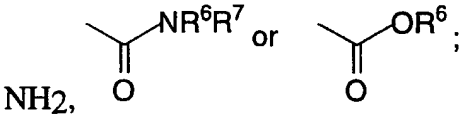
wherein

R^{1a} and R^{1c} are independently selected from: hydrogen, C_3-C_{10} cycloalkyl, R^8O-, -$N(R^8)_2$, F or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, R^8O-, -$N(R^8)_2$, F or C_2-C_6 alkenyl,
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, R^8O- and -$N(R^8)_2$;

R^{2a} is selected from selected from: H; C_1-C_6 alkyl,



NH_2, or ;

R^{3a} and R^{3b} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-$C(NR^8)$-, CN, NO_2, $R^8C(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-$C(NR^8)$-, CN, $R^8C(O)$-, N_3, $-N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^4 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^{5a} and R^{5b} are independently hydrogen, C_1-C_6 alkyl, cyclopropyl, trifluoromethyl and halogen;

R^6 and R^7 are independently selected from:
H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with one or two:
a) C_{1-4} alkoxy,
b) halogen, or
c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^8-, O, -N(R^8)-, or -S(O)$_m$;

V is selected from:
a) hydrogen,
b) heterocycle selected from pyrrolidinyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is S(O)$_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is S(O)$_m$;

X is a bond, -S(O)$_m$-, O or -C(=O)-;

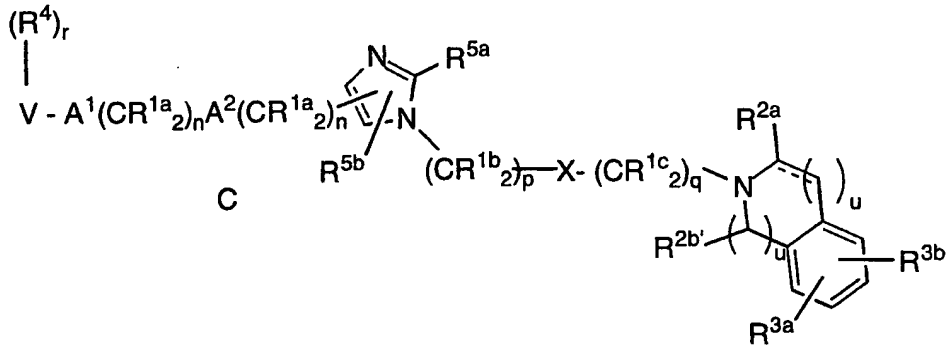
Y is selected from: CR^{2a}, C=O, C=NH or N;

Z is selected from: CR^{2a}, C=O or N;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 1, 2 or 3;
q is 0, 1 or 2, provided that q is not 0 or 1 if X is O;
r is 0 to 5, provided that r is 0 when V is hydrogen; and
y is 1 or 2;

or an optical isomer or pharmaceutically acceptable salt thereof.

7. The compound according to Claim 2 which inhibits farnesyl-protein transferase of the formula C:



C

wherein:

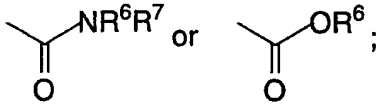
R^{1a} and R^{1c} are independently selected from: hydrogen, C_3-C_{10} cycloalkyl, R^8O-, -$N(R^8)_2$, F or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, R^8O-, -$N(R^8)_2$, F or C_2-C_6 alkenyl,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, R^8O- and -$N(R^8)_2$;

R^{2a} and $R^{2b'}$ are independently selected from selected from: H; C_1-C_6 alkyl,  ;

R^{3a} and R^{3b} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-$C(NR^8)$-, CN, NO_2, $R^8C(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-$C(NR^8)$-, CN, $R^8C(O)$-, N_3, -$N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^4 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6

perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^{5a} and R^{5b} are independently hydrogen, C_1-C_6 alkyl, cyclopropyl, trifluoromethyl and halogen;

R^6 and R^7 are independently selected from:
H; C_1-$_4$ alkyl, C_3-$_6$ cycloalkyl, aryl, heterocycle, unsubstituted or substituted with one or two:
a) C_1-$_4$ alkoxy,
b) halogen, or
c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, $-C(O)NR^8$-, O, $-N(R^8)$-, or $-S(O)_m$;

V is selected from:
a) hydrogen,
b) heterocycle selected from pyrrolidinyl, imidazolinyl, pyridinyl, thiazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,
c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl, and

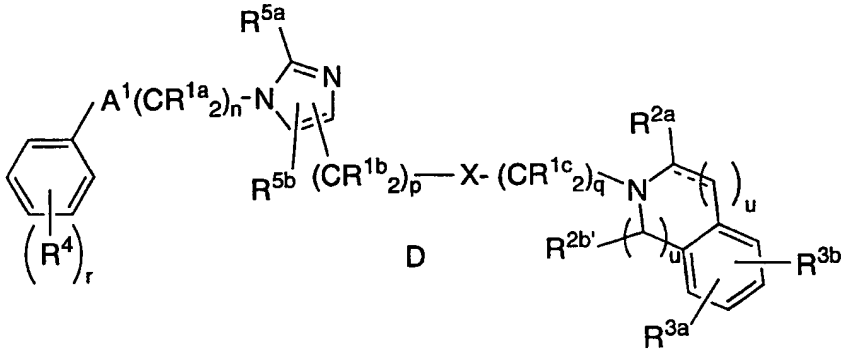
provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

X is a bond, $-S(O)_m-$, O or -C(=O)-;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond or O;
q is 0, 1 or 2, provided that q is not 0 or 1 if X is O;
r is 0 to 5, provided that r is 0 when V is hydrogen; and
u is independently 0 or 1;

or an optical isomer or pharmaceutically acceptable salt thereof.

8. The compound according to Claim 5 which inhibits farnesyl-protein transferase of the formula D:



D

wherein:

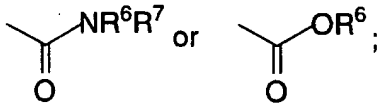
R^{1a} and R^{1c} are independently selected from: hydrogen, C_3-C_{10} cycloalkyl or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, R^8O-, -$N(R^8)_2$, F or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, R^8O-, or -$N(R^8)_2$;

R^{2a} and $R^{2b'}$ are independently selected from selected from: H; C_1-C_6 alkyl,  ;

R^{3a} and R^{3b} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-$C(NR^8)$-, CN, NO_2, $R^8C(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-$C(NR^8)$-, CN, $R^8C(O)$-, N_3, -$N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^4 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^{5a} and R^{5b} are independently hydrogen, ethyl, cyclopropyl or methyl;

R^6 and R^7 are independently selected from:
H; C_1-4 alkyl, C_3-6 cycloalkyl, aryl, heterocycle, unsubstituted or substituted with one or two:
a) C_1-4 alkoxy,
b) halogen, or
c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

A^1 is selected from: a bond, -C(O)-, O, -$N(R^8)$-, or -$S(O)_m$;

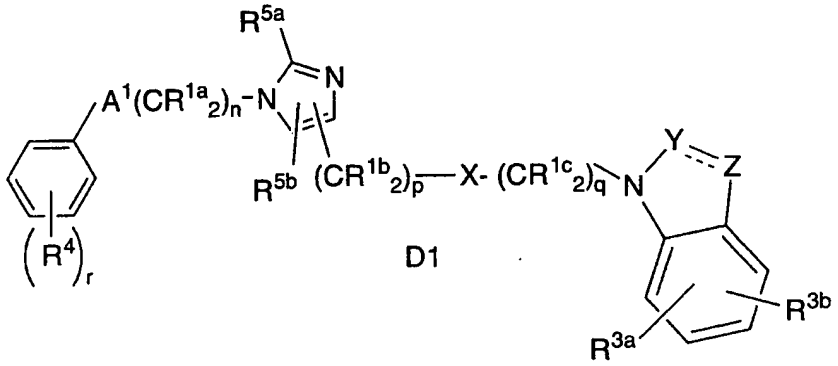
X is a bond, -$S(O)_m$-, O or -C(=O)-;

n is 0, 1 or 2; provided that n is not 0 or 1 if A^1 is a bond, O, -$N(R^8)$-, or $S(O)_m$;
m is 0, 1 or 2;
p is 0, 1, 2, 3 or 4;
q is 0, 1 or 2, provided that q is not 0 or 1 if X is O;
r is 1 or 2; and

u is independently 0 or 1;

or an optical isomer or pharmaceutically acceptable salt thereof.

9. The compound according to Claim 6 which inhibits farnesyl-protein transferase of the formula D1:



D1

wherein

R^{1a} and R^{1c} are independently selected from: hydrogen, C_3-C_{10} cycloalkyl or C_1-C_6 alkyl;

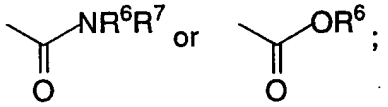
R^{1b} is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, R^8O-, -$N(R^8)_2$, F or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, R^8O-, or -$N(R^8)_2$;

R^{2a} is selected from selected from: H; C_1-C_6 alkyl, NH_2,



R^{3a} and R^{3b} are independently selected from:

a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-$C(NR^8)$-, CN, NO_2, $R^8C(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-,
c) unsubstituted C_1-C_6 alkyl,
d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-$C(NR^8)$-, CN, $R^8C(O)$-, N_3, $-N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^4 is independently selected from:
a) hydrogen,
b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^{5a} and R^{5b} are independently hydrogen, ethyl, cyclopropyl or methyl;

R^6 and R^7 are independently selected from:
H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with one or two:
a) C_{1-4} alkoxy,

b) halogen, or
c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

A^1 is selected from: a bond, -C(O)-, O, -N(R^8)-, or -S(O)$_m$;

X is a bond, -S(O)$_m$-, O or -C(=O)-;

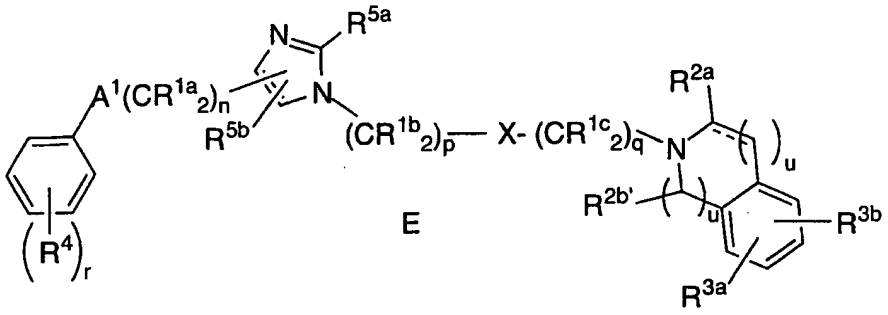
Y is selected from: CR^{2a}, C=NH or N;

Z is selected from: CR^{2a}, or N; provided that at least Y or Z is N;

n is 0, 1 or 2; provided that n is not 0 or 1 if A^1 is a bond, O, -N(R^8)-, or S(O)$_m$;
m is 0, 1 or 2;
p is 0, 1, 2, 3 or 4;
q is 0, 1 or 2, provided that q is not 0 or 1 if X is O;
r is 1 or 2; and
y is 1 or 2;

or an optical isomer or pharmaceutically acceptable salt thereof.

10. The compound according to Claim 7 which inhibits farnesyl-protein transferase of the formula E:



E

wherein:

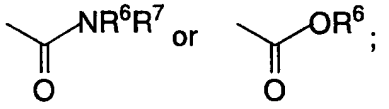
R^{1a} and R^{1c} are independently selected from: hydrogen, R^8O-, $-N(R^8)_2$, F, C_3-C_{10} cycloalkyl or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, R^8O-, $-N(R^8)_2$, F or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, R^8O-, or $-N(R^8)_2$;

R^{2a} and $R^{2b'}$ are independently selected from selected from: H; C_1-C_6 alkyl,  ;

R^{3a} and R^{3b} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-

$C(NR^8)$-, CN, NO_2, $R^8C(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-$C(NR^8)$-, CN, $R^8C(O)$-, N_3, $-N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^4 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^{5a} and R^{5b} are independently hydrogen, ethyl, cyclopropyl or methyl;

R^6 and R^7 are independently selected from:

H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with one or two:

a) C_{1-4} alkoxy,

b) halogen, or

c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

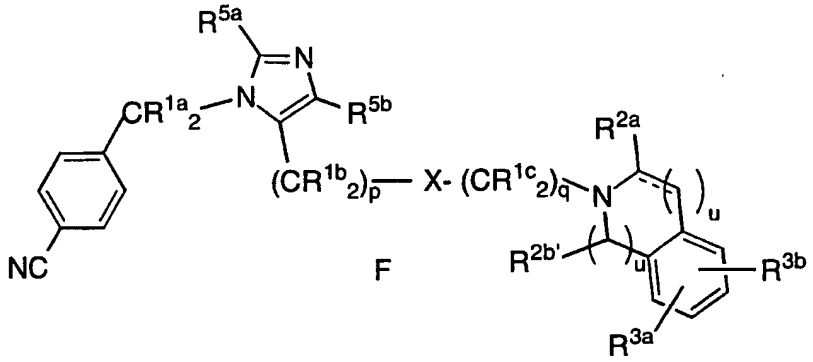
R^9 is independently selected from C_1-C_6 alkyl and aryl;

X is a bond, -S(O)m-, O or -C(=O)-;

n is 0 or 1;
m is 0, 1 or 2;
p is 0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond or O;
q is 0, 1 or 2, provided that q is not 0 or 1 if X is O;
r is 1 or 2; and
u is independently 0 or 1;

or an optical isomer or pharmaceutically acceptable salt thereof.

11. The compound according to Claim 8 which inhibits farnesyl-protein transferase of the formula F:



F

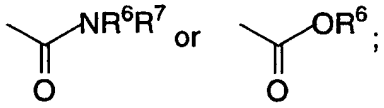
wherein:

R^{1a} and R^{1c} are independently selected from: hydrogen, C_3-C_{10} cycloalkyl or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, R^8O-, -$N(R^8)_2$ or F,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, R^8O-, or -$N(R^8)_2$;

R^{2a} and $R^{2b'}$ are independently selected from selected from: H; C_1-C_6 alkyl,  ;

R^{3a} and R^{3b} are independently selected from:
a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-$C(NR^8)$-, CN, NO_2, $R^8C(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-,
c) unsubstituted C_1-C_6 alkyl,
d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-$C(NR^8)$-, CN, $R^8C(O)$-, N_3, -$N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^{5a} and R^{5b} are independently hydrogen, ethyl, cyclopropyl or methyl;

R^6 and R^7 are independently selected from:
H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with one or two:
a) C_{1-4} alkoxy,
b) halogen, or

c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

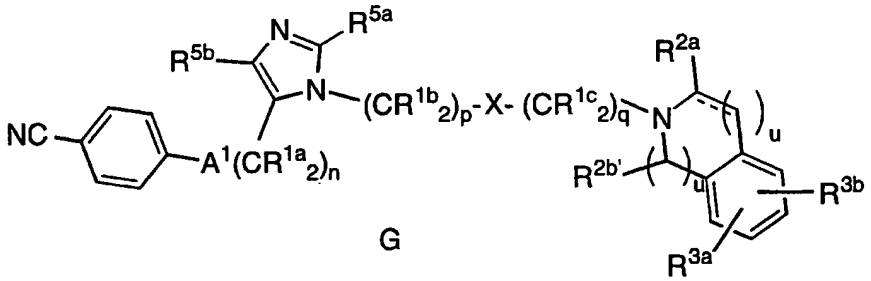
R^9 is independently selected from C_1-C_6 alkyl and aryl;

X is a bond, -S(O)$_m$-, O or -C(=O)-;

m is 0, 1 or 2;
p is 0, 1, 2, 3 or 4;
q is 0, 1 or 2, provided that q is not 0 or 1 if X is O; and
u is independently 0 or 1;

or an optical isomer or pharmaceutically acceptable salt thereof.

12. The compound according to Claim 10 which inhibits farnesyl-protein transferase of the formula G:



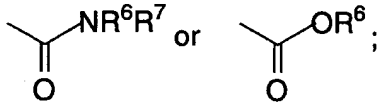
G

wherein:

R^{1a} and R^{1c} are independently selected from: hydrogen, R^8O-, -N(R^8)$_2$, F, C_3-C_{10} cycloalkyl or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle or C_3-C_{10} cycloalkyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, R^8O-, or $-N(R^8)_2$;

R^{2a} and $R^{2b'}$ are independently selected from selected from: H; C_1-C_6 alkyl,  ;

R^{3a} and R^{3b} are independently selected from:
a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3-C_{10} cycloalkyl, unsubstituted or substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^9C(O)O$-, $R^8{}_2N$-$C(NR^8)$-, CN, NO_2, $R^8C(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-,
c) unsubstituted C_1-C_6 alkyl,
d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^9O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, $(R^8)_2NC(O)$-, $R^8{}_2N$-$C(NR^8)$-, CN, $R^8C(O)$-, N_3, $-N(R^8)_2$, and $R^9OC(O)$-NR^8-;

R^{5a} and R^{5b} are independently hydrogen, ethyl, cyclopropyl or methyl;

R^6 and R^7 are independently selected from:
H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with one or two:
a) C_{1-4} alkoxy,

b) halogen, or
c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

A^1 is selected from: a bond, -C(O)-, O, -N(R^8)-, or -S(O)$_m$;

X is a bond, -S(O)$_m$-, O or -C(=O)-;

m is 0, 1 or 2;
n is 0, 1 or 2; provided that n is not 0 if A^1 is a bond, O, -N(R^8)-, or S(O)$_m$;
p is 1, 2 or 3;
q is 0, 1 or 2, provided that q is not 0 or 1 if X is O; and
u is independently 0 or 1;

or an optical isomer or pharmaceutically acceptable salt thereof.

13. A compound which inhibits farnesyl-protein transferase which is:

7-Bromo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

2-(1-(4-Cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

5,7-Dichloro-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

3(S)-Carboethoxy-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

3(R)-Carboethoxy-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

7-Nitro-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

7-Amino-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline tris

7-Acetamido-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

7-Iodo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

5-Bromo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

5-(2,4-Dichlorophenyl)-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

5-(4-Cyanobenzyl) -2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

5-(2-(3-Tolyl)vinyl)-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

5-(2-(3-Tolyl)ethyl)-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

7-Phenyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

7-(2-Tolyl)-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

N-(2,3-Dimethylphenyl)-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxamide

N-(3-Chlorobenzyl) 2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxamide

N-(3-Chlorobenzyl),N-methyl 2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxamide

N-(2,3-Dimethylphenyl)-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline-3(R)-carboxamide

3(S)-Carboethoxy-7-phenyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

3(S)-Carboxylic acid-7-phenyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

N-(3-chlorobenzyl) 7-phenyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline-3(s)-carboxamide

3(S)-Hydroxymethyl-7-phenyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

1(R,S)-n-Butyl-7-bromo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

1-(1-(4-Cyanobenzyl)-5-imidazolylmethyl)indole

5-Bromo-1-(1-(4-cyanobenzyl)-5-imidazolylmethyl)indole

4-Bromo-1-(1-(4-cyanobenzyl)-5-imidazolylmethyl)indole

4-Phenyl-1-(1-(4-cyanobenzyl)-5-imidazolylmethyl)indole

4-(2-Methylphenyl)-1-(1-(4-cyanobenzyl)-5-imidazolylmethyl)indole

6-Bromo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-3,4-dihydro-1(1H)-isoquinolinone

6-Bromo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline

7-Bromo-2-(1-(4-cyanobenzyl)-5-imidazolylacetyl)-1,2,3,4-tetrahydroisoquinoline

5-Chloro-2-carboethoxy-1-(1-(4-cyanobenzyl)-5-imidazolylmethyl)indole

1-(4-cyanobenzyl)-5-(1-indolinylmethyl)imidazole
1-(4-cyanobenzyl)-5-(1-indazolylmethyl)imidazole

1-(4-cyanobenzyl)-5-(1-tetrahydroquinolinylmethyl)imidazole

5-(1-benzotriazolylmethyl)-1-(4-cyanobenzyl)imidazole

5-(1-benzoimidazolylmethyl)-1-(4-cyanobenzyl)imidazole

5-[1-(7-azaindolyl)methyl]-1-(4-cyanobenzyl)imidazole
5-[1-(4-azabenzimidazolyl)methyl]-1-(4-cyanobenzyl)imidazole

1-(4-cyanobenzyl)-5-(2-tetrahydroisoquinolinylmethyl)imidazole

5-(2-benzotriazolylmethyl)-1-(4-cyanobenzyl)imidazole

1-(4-cyanobenzyl)-5-(1-isatinylmethyl)imidazole

5-[1-(5-azabenzimidazolyl)methyl]-1-(4-cyanobenzyl)imidazole

5-[3-(5-azabenzimidazolyl)methyl]-1-(4-cyanobenzyl)imidazole

4-{5-[4-(3-Bromophenyl)-4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridin-1-ylmethyl]imidazol-1-ylmethyl}benzonitrile

6,7-Dimethoxy-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)1,2,3,4-tetrahydroisoquinoline

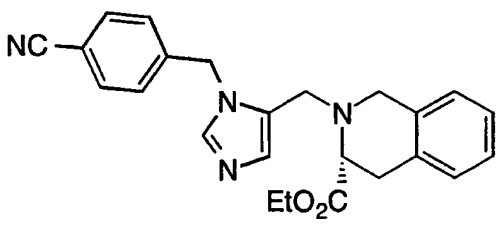
1(R,S)-(2-Phenethyl)-6-methoxy-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline
1-(4-Cyanobenzyl)-5-(2-amino-1 -benzimidazolylmethyl)imidazole

1-(4'-cyanobenzyl)-5-(2-amino-1-(3-benzyl-2-imino-1-benzimidazolylmethyl)imidazole

or an optical isomer or a pharmaceutically acceptable salt thereof.

14. The compound according to Claim 13 which is:

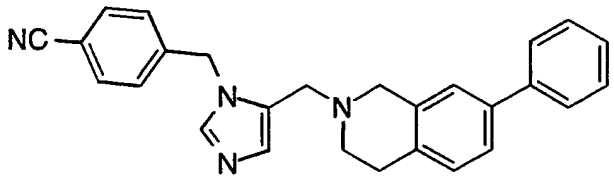
3(R)-Carboethoxy-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline



or an optical isomer or a pharmaceutically acceptable salt thereof.

15. The compound according to Claim 13 which is:

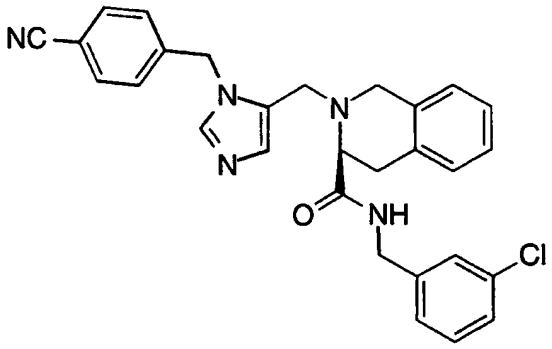
7-Phenyl-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline



or a pharmaceutically acceptable salt thereof.

16. The compound according to Claim 13 which is:

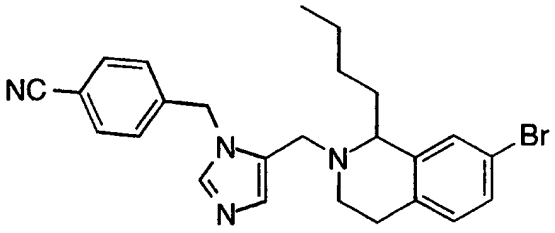
N-(3-Chlorobenzyl) 2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxamide



or an optical isomer or a pharmaceutically acceptable salt thereof.

17. The compound according to Claim 13 which is:

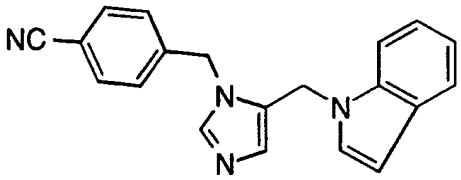
1(R,S)-n-Butyl-7-bromo-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-1,2,3,4-tetrahydroisoquinoline



or an optical isomer or a pharmaceutically acceptable salt thereof.

18. The compound according to Claim 13 which is:

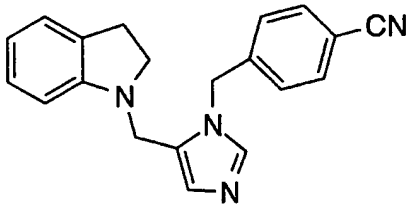
1-(1-(4-Cyanobenzyl)-5-imidazolylmethyl)indole



or an optical isomer or a pharmaceutically acceptable salt thereof.

19. The compound according to Claim 13 which is:

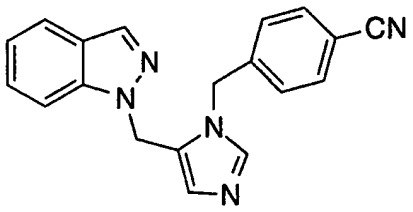
1-(4-cyanobenzyl)-5-(1-indolinylmethyl)imidazole



or an optical isomer or a pharmaceutically acceptable salt thereof.

20. The compound according to Claim 13 which is:

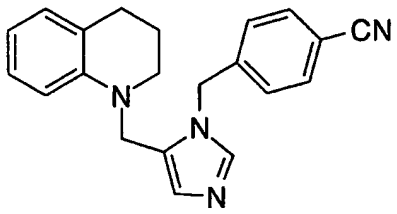
1-(4-cyanobenzyl)-5-(1-indazolylmethyl)imidazole



or an optical isomer or a pharmaceutically acceptable salt thereof.

21. The compound according to Claim 13 which is:

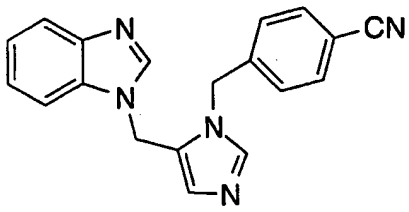
1-(4-cyanobenzyl)-5-(1-tetrahydroquinolinylmethyl)imidazole



or an optical isomer or a pharmaceutically acceptable salt thereof.

22. The compound according to Claim 13 which is:

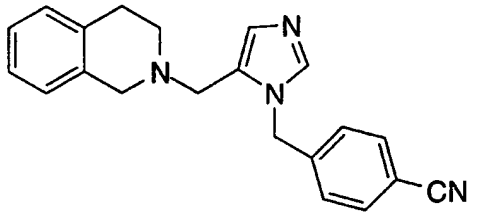
5-(1-benzoimidazolylmethyl)-1-(4-cyanobenzyl)imidazole



or an optical isomer or a pharmaceutically acceptable salt thereof.

23. The compound according to Claim 13 which is:

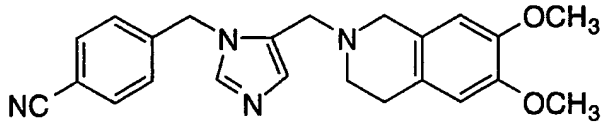
1-(4-cyanobenzyl)-5-(2-tetrahydroisoquinolinylmethyl)imidazole



or an optical isomer or a pharmaceutically acceptable salt thereof.

24. The compound according to Claim 13 which is:

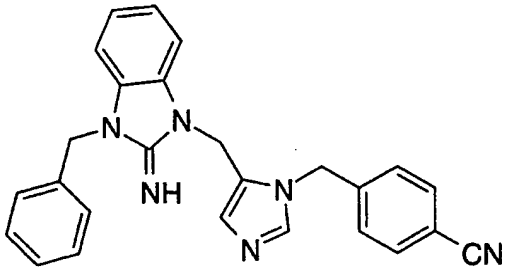
6,7-Dimethoxy-2-(1-(4-cyanobenzyl)-5-imidazolylmethyl)1,2,3,4-tetrahydroisoquinoline



or an optical isomer or a pharmaceutically acceptable salt thereof.

25. The compound according to Claim 13 which is:

1-(4'-cyanobenzyl)-5-(2-amino-1-(3-benzyl-2-imino-1-benzimidazolylmethyl)imidazole



or an optical isomer or a pharmaceutically acceptable salt thereof.

26. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 1.

27. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 2.

28. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 5.

29. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 7.

30. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 13.

31. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 26.

32. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 27.

33. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need

thereof a therapeutically effective amount of a composition of Claim 28.

34. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 29.

35. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 30.

36. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 26.

37. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 27.

38 A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 28.

39. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 29.

40. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 30.

41. A method for treating neurofibromin benign proliferative disorder which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 27.

42. A method for treating blindness related to retinal vascularization which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 27.

43. A method for treating infections from hepatitis delta and related viruses which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 27.

44. A method for preventing restenosis which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 27.

45. A method for treating polycystic kidney disease which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 27.

46. A pharmaceutical composition made by combining the compound of Claim 1 and a pharmaceutically acceptable carrier.

47. A pharmaceutical composition made by combining the compound of Claim 2 and a pharmaceutically acceptable carrier.

48. A process for making a pharmaceutical composition comprising combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

49. A process for making a pharmaceutical composition comprising combining a compound of Claim 2 and a pharmaceutically acceptable carrier.

SEQUENCE LISTING

<110> Ciccarone, Terrence M.
Halczenko, Wasyl
Hutchinson, John H.
Lumma, William C. Jr.
Stokker, Gerald E.
Stump, Craig A.
Williams, Theresa M.
Merck & Co., Inc.

<120> INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

<130> 19850Y2

<150> 08/985,320
<151> 1997-12-04

<160> 26

<170> FastSEQ for Windows Version 3.0

<210> 1
<211> 4
<212> PRT
<213> Homosapien

<400> 1
Cys Val Ile Met
1

<210> 2
<211> 4
<212> PRT
<213> Homosapien

<400> 2
Cys Val Leu Leu
1

<210> 3
<211> 4
<212> PRT
<213> Homosapien

<400> 3
Cys Val Val Met
1

<210> 4
<211> 4
<212> PRT
<213> Homosapien

<400> 4
Cys Ile Ile Met
1

<210> 5
<211> 4
<212> PRT
<213> Homosapien

<400> 5
Cys Leu Leu Leu
1

<210> 6
<211> 4
<212> PRT
<213> Homosapien

<400> 6
Cys Gln Leu Leu
1

<210> 7
<211> 4
<212> PRT
<213> Homosapien

<400> 7
Cys Ser Ile Met
1

<210> 8
<211> 4
<212> PRT
<213> Homosapien

<400> 8
Cys Ala Ile Met
1

<210> 9
<211> 4
<212> PRT
<213> Homosapien

<400> 9
Cys Lys Val Leu
1

<210> 10
<211> 4
<212> PRT
<213> Homosapien

<400> 10
Cys Leu Ile Met

1

<210> 11
<211> 4
<212> PRT
<213> Homosapien

<400> 11
Cys Val Leu Ser
1

<210> 12
<211> 4
<212> PRT
<213> Homosapien

<400> 12
Cys Ala Ile Leu
1

<210> 13
<211> 15
<212> PRT
<213> Homosapien

<400> 13
Gly Lys Lys Lys Lys Lys Lys Ser Lys Thr Lys Cys Val Ile Met
1 5 10 15

<210> 14
<211> 86
<212> DNA
<213> Artificial Sequence

<220>
<223> completely synthesized

<400> 14
tctcctcgag gccaccatgg ggagtagcaa gagcaagcct aaggacccca gccagcgccg 60
gatgacagaa tacaagcttg tggtgg 86

<210> 15
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> completely synthesized

<400> 15
cacatctaga tcaggacagc acagacttgc agc 33

<210> 16
<211> 41
<212> DNA
<213> Artificial Sequence

<220>
<223> completely synthesized

<400> 16
tctcctcgag gccaccatga cagaatacaa gcttgtggtg g 41

<210> 17
<211> 38
<212> DNA
<213> Artificial Sequence

<220>
<223> completely synthesized

<400> 17
cactctagac tggtgtcaga gcagcacaca cttgcagc 38

<210> 18
<211> 38
<212> DNA
<213> Artificial Sequence

<220>
<223> completely synthesized

<400> 18
gagagaattc gccaccatga cggaatataa gctggtgg 38

<210> 19
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> completely synthesized

<400> 19
gagagtcgac gcgtcaggag agcacacact tgc 33

<210> 20
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> completely synthesized

<400> 20
ccgccggcct ggaggagtac ag 22

<210> 21
<211> 38
<212> DNA
<213> Artificial Sequence

<220>
<223> completely synthesized

<400> 21
gagagaattc gccaccatga ctgagtacaa actggtgg 38

<210> 22
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> completely synthesized

<400> 22
gagagtcgac ttgttacatc accacacatg gc 32

<210> 23
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> completely synthesized

<400> 23
gttggagcag ttggtgttgg g 21

<210> 24
<211> 38
<212> DNA
<213> Artificial Sequence

<220>
<223> completely synthesized

<400> 24
gagaggtacc gccaccatga ctgaatataa acttgtgg 38

<210> 25
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> completely synthesized

<400> 25
ctctgtcgac gtatttacat aattacacac tttgtc 36

<210> 26
<211> 24
<212> DNA
<213> Artificial Sequence

<220>

<223> completely synthesized

<400> 26
gtagttggag ctgttggcgt aggc 24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/25352

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 401/02; A61K 31/415, 31/47

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/314, 339, 394, 397; 546/148, 273.4, 277.1;v548/304.7, 335.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS COMPUTER SEARCH 1966-TO DATE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X - Y	US 5,569,768 A (BOYD et al) 29 October 1996, col. 37, lines 46 and 47.	1 and 6 --- 1 and 6
A	US 5,439,918 A (de SOLMS et al.) 08 August 1995, see entire document.	1-49

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 04 FEBRUARY 1999	Date of mailing of the international search report 16 FEB 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ZINNA N. DAVIS Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/25352

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/314, 339, 394, 397; 546/148, 273.4, 277.1; 548/304.7, 335.5